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SMJ

Second Edition

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"Where Finbarr taught let Munster learn."

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Foreword

From the depth of the 15th century flourished perhaps the greatest rebirth of ideas, communication, science, art and culture.

From the depth of the 15th century flourished perhaps the greatest rebirth of ideas, communication, science, art and culture. The Renaissance was the beginning of what would become known as a movement towards perseverance capturing the essence of human life and serving as an ultimate memorandum of hope and creativity that remains alive to this day. Interestingly enough, many of the scholars that examined the production of the era came to be known as "humanists" while studying the peculiar human behaviour overtime became known as the study of humanities. As we delve into the world of medical research, exploring from the intricate level of a DNA base to the ultimate complexity of human systems, we cannot help but notice the similarity between the curious student researcher that bends over their lab desk, overwhelmed by the vast possibility of gaining knowledge to that of the renaissance painter, that carefully stroked their brush, perfecting the anatomical art of human life. As well, the scholars of Medicine have long believed that perfection in the field is achieved through coexistence of science and art and that one cannot simply be favored over the other when dealing with the human body.

Undoubtedly, the onset of the pandemic has marked a despondent time for most of us, and the second edition of the student medical journal brings with it the transition to another year of hope and prosperity. After a successful publication of UCC's very first student medical journal, UCC Medical Research and Technology Society presents to you another edition, appreciating the student hardship and contribution during these times. As students and staff transition back to a life of normality, we cannot help but notice how quickly the human mind consents to a certain lifestyle, and the mere thought of returning to a former life suddenly seems novel and intimidating. Keeping this in mind, the journal team believes that nothing marks a better illustration of transition than the renaissance period. Likewise, medical research has always been an intimidating and an out-of-reach concept. We hope that through this publication, we can further encourage student involvement in research and lift uncertainties in young researchers.

We would like to thank the School of Medicine for their utmost support towards the formation of this journal. As well, the peer reviewers and faculty that dedicated their precious time towards reviewing each submission thoroughly. Additionally, we would like to express our utmost gratitude to our student contributors that took the time to incorporate peer and faculty advice in their submissions. Finally, we want to thank our readers for making our publications possible. UCC MRT and the student journal team wishes you an interesting read and a joyous year ahead.

Kind Regards,
Kashaf Aamer
Lena Dablouk
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Adina Elena Zagoneanu

Address

Dr. Collete Hand,
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Thanks to the committee for inviting me to write in this second Edition of the Student Medical Journal. It is really encouraging to see the promotion and awareness of research embedded in our undergraduate programmes from an early stage.

When I think about what research is and what it means, I always return to one word: curiosity. Research is asking questions, like why does this happen? Why does this not happen? Children exhaust parents with endless questions; why, what, how and how long? Then, usually the questions stop. Maybe we lose the confidence to ask questions, perhaps we think we know all the answers or that we should know them. A researcher recognises that there is so much that we don't know and that it is necessary to question and challenge.

Undergraduate medical and science programmes train students to structure questions. They guide how to frame or ask a question and importantly, how to think about the ways in which to best answer it. This applies across all types of research. What is your question, how can it be answered and what do we learn? Research is never-ending; almost always the answer leads to more questions. For some people this is a frustrating aspect of research because it doesn't end. For others, that's the joy of it, that you are constantly learning, constantly thinking of the next question and how to answer it, developing the hypothesis as you progress.

I believe strongly in the benefits of engaging with research in your undergraduate programme. Think beyond the structured elements within your course such as a literature review and seek out other opportunities. A summer project is an excellent entry point into research. There are several funding sources to encourage this type of early research activity eg both Health Research Board (HRB) and Wellcome Trust provide summer studentships. The UCC College of Medicine and Health (CoMH) offers Summer Undergraduate Research Experience (SURE) awards and the Medical and Health Sciences programme provide Translational Research Internship (TRAIN) funding. Consider people who have interested or inspired you in your course or those working on a topic that interests you. Check out CoMH Research for a list of institutes, centres and units. Approach lecturers or researchers directly and ask about research opportunities. Research can seem like a very different world, find someone who will encourage and guide you.

Participating in research from an early stage brings many benefits, both short and long term. Remember that we will all encounter research, regardless of whether it is something that we 'do' or not, it is in everything; the latest Covid-19 vaccine, the newest treatment for cancer. To utilise that information, we need to understand it. One of the biggest impacts of becoming research active is that the experience gives access to another way of thinking, another perspective. It is not restricted only to what you are studying but gives a broader view on any questions you approach or papers that you read. Research experience allows you to challenge or critique information or results more proficiently.

Research in a laboratory setting has the additional benefit of providing practical skills. This may enhance future work or research opportunities. More importantly though, once you have worked in a lab your way of approaching techniques changes. You start to question more; is that the right control to use or is that a good explanation of the results. It provides the confidence to question.

There is nothing like the highs of research, discovering something that wasn't known before or sometimes it is just that the experiment finally works! The flip side is that it can be difficult when things do not work as expected but part of the process is figuring out why. If we know the answer, it isn't research, is it?

Keep wondering why, keep questioning, keep reading. Find a mentor who will encourage and guide you. If you are really lucky, you will find a group of like-minded people who become your supporters and with whom you can share the challenges and successes of the research process.
There is always an appropriate quote from Dr Seuss.

"It's high time you were shown
That you really don't know
All there is to be known."
- On Beyond Zebra, Dr Seuss

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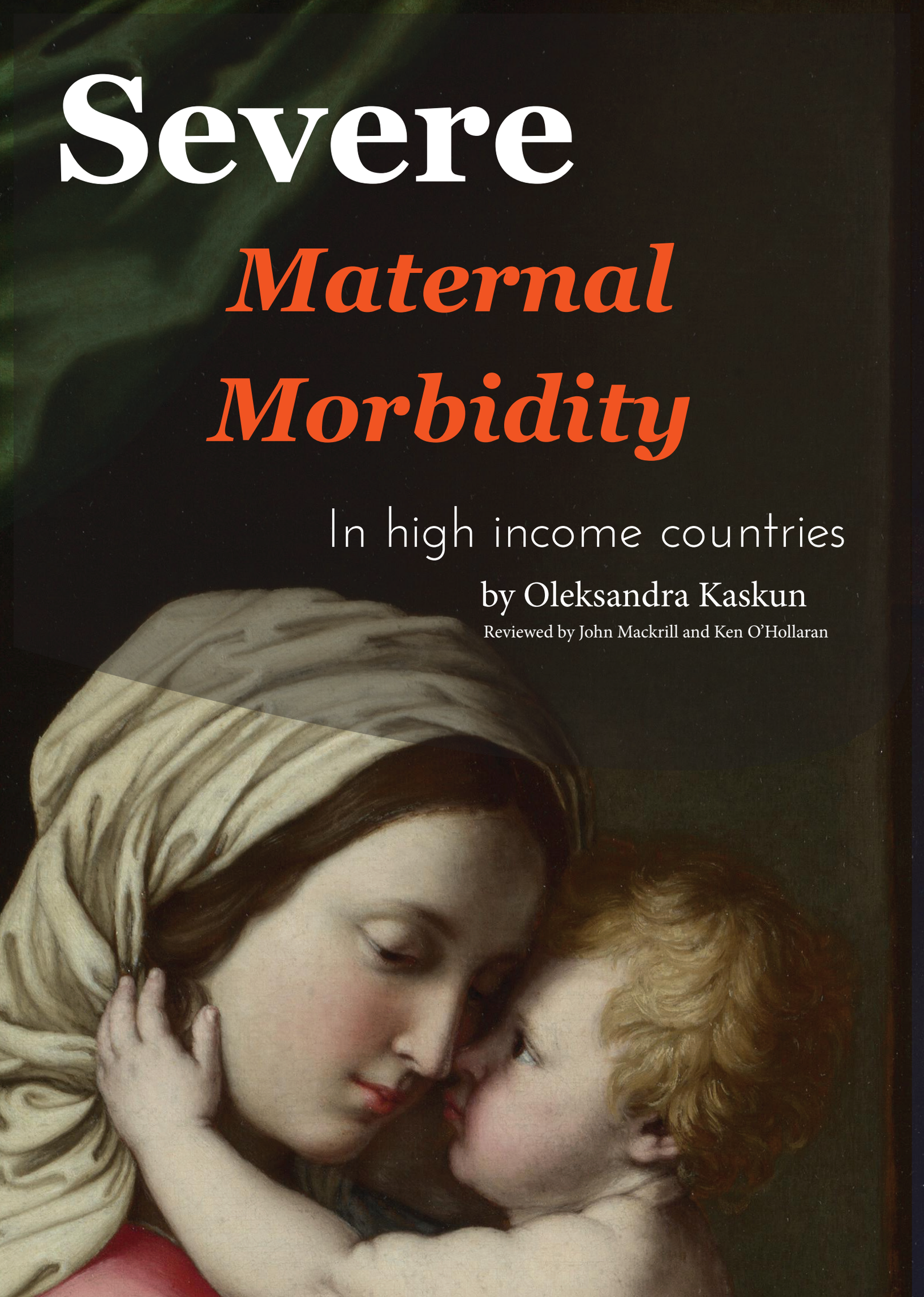
Severe *Maternal Morbidity*

In high income countries

by Oleksandra Kaskun

Reviewed by John Mackrill and Ken O'Hollaran



Abstract

Introduction

With declining maternal mortality rates in high income countries (HICs), severe maternal morbidity (SMM) is becoming an important quality measure of maternal care. However, there is no international consensus on the definition and types of SMM. This study aims to critically analyze published literature on SMM in HICs.

Objectives

To compare definitions and criteria used to identify SMM, and to identify the main types and risk factors contributing to SMM in eight HICs.

Methods

Three databases were searched, results were filtered, and ten studies were critically appraised.

Results

Six of the articles discussed SMM identification criteria and proposed definition modifications. Longer hospital stay and admission to intensive care unit were suggested as additional criteria. Disease-based criteria was shown to be superior to organ dysfunction criteria. Seven articles detailed common types of SMM as severe haemorrhage, hypertensive disorders, and pre-eclampsia/eclampsia. Six articles described SMM risk factors, of which advanced maternal age and caesarean delivery were most common.

Discussion

This literature review identified disease-based criteria and Canadian study criteria as promising measures of SMM. It also identified several types and risk factors of SMM common between HICs. These findings can help physicians identify women at risk of SMM. The study is however limited to eight HICs and ten studies. Further research should aim to investigate how the measures compare with previous sources of criteria, and to discern the association of weight and race risk factors with SMM.

Introduction

Maternal health is an important measure of a country's overall socioeconomic progress.1

As maternal mortality rates have declined precipitously in high income countries (HICs) to the level of becoming rare events, the World Health Organization (WHO) has suggested tracking the incidence of severe maternal morbidity (SMM) (synonymous with maternal near miss) as a quality indicator of obstetric care.[2] The Maternal Morbidity Working Group organised by the WHO defines maternal morbidity as any chronic or acute health condition which can be due to or aggravated by pregnancy or childbirth and has a negative impact on the woman's wellbeing.[1]

In contrast, there is no standardised definition of SMM, and no internationally consistent case identification criteria. SMM is usually described as a "maternal near miss" case, the near death of a woman who survived a complication relating to pregnancy or childbirth or within 42 days of termination of pregnancy[3,4]. The WHO has proposed guidelines in 2011 for identifying maternal near miss cases based on clinical criteria, laboratory markers, and management proxies.[4] They included five potentially life-threatening conditions (severe postpartum haemorrhage, severe pre-eclampsia, eclampsia, sepsis, and ruptured uterus), a range of critical interventions or the admission to intensive care unit, as well as seven types of organ dysfunction as near miss criteria.[4] However, varying definitions of SMM and variations of case inclusion criteria have been used by hospitals and countries around the world. These variations can be the inclusion or exclusion of pre-pregnancy conditions in the definition of maternal morbidity, or suggested expansions to either the 2011 WHO list or other country-specific lists of criteria.[The non-uniformity of the definition and the lack of consensus on inclusion criteria for identifying SMM cases hampers comparative analysis and determination of the true global burden of SMM.

The rates of SMM have not seen similar declines as have maternal mortality rates, and in some HICs such as the USA, they have increased. According to the Centers for Disease Control and Prevention (CDC), the annual prevalence of SMM in the United States (U.S.) has more than doubled between 1998 and 2014.[5] The apparent increase in SMM can be attributed to the changing characteristics of women giving birth over the last few decades – advanced maternal age, obesity, co-morbidities such as diabetes or hypertension, as well as the increased occurrence of caesarean delivery. These factors have been associated with higher SMM risk,[5] but the increase can also be due to changes in SMM identification criteria.

Box 1:
List of Abbreviations

BMI: Body mass index
CCI: Canadian Classification of Health Interventions
CDC: Centers for Disease Control and Prevention
CWIUH: Coombe Women and Infants University Hospital
DIC: Diffuse intravascular coagulation
HICs: High income countries
HDU: high dependency unit
ICD: International Classification of Diseases
ICU: Intensive care unit
KEMH: King Edward Memorial Hospital
SLE: Systemic lupus erythematosus
SMM: Severe maternal morbidity
WHO: World Health Organization

Aims and Objectives

The aim of this study was to systematically analyse and critically appraise published literature on SMM in obstetrics in HICs with the specific objectives as follow:

1. To compare the definitions and criteria used to identify SMM in HICs.
2. To identify the main types of SMM in different countries.
3. To identify the principal risk factors contributing to SMM.

Methods

Search Strategy

An electronic search was performed using three databases, PubMed, Cumulative Index of Nursing and Allied Health Literature (CINAHL), and Scopus, to identify relevant literature to answer the objectives of this review.

PubMed:

1. Severe maternal morbidity:
   "severe maternal morbidity"[text word] OR "Near Miss, Healthcare"[Mesh] OR "maternal near miss"[text word] OR "maternal near-miss"[text word] OR near-miss[text word] OR "near miss"[text word]
   AND
2. High income countries:
   "Developed Countries"[Mesh] OR "high income countr*"[text word] OR "developed countr*"[text word]

Results were filtered for publication in the last 10 years, free full text availability, and availability in English.

CINAHL:

1. Severe maternal morbidity:
   ("severe maternal morbidity" OR "maternal near miss" OR "maternal near-miss" OR near-miss OR "near miss") [all text]
   AND
2. High income countries:
   ("Developed Countr*" OR "high income countr*")[all text]

Results were filtered for publication between 2010 and 2020 inclusive, free full text availability, availability in English, and academic journal type.

Scopus:

1. Severe maternal morbidity:
   ALL ("severe maternal morbidity" OR "maternal near miss" OR "maternal near-miss" OR near-miss OR "near miss")
   AND
2. High income countries:
   ALL ("Developed Countr*" OR "high income countr*")

Results were filtered for publication between 2010-2020 inclusive, free full text availability, availability in English and document type 'Article'. Studies greater than ten years old were excluded to limit the number of results obtained.

Category	Inclusion Criteria	Exclusion Criteria
Publication Date	2010-2020	Prior to 2010
Text Availability	Free full text available	Unavailable free full text
Language	English	Not in English
Article Type	Original research in academic journals	Systematic review Poster/conference Protocol Commentary article Literature Review Case Study Narrative Review
Research Location	Current HICs as defined by World Bank	Not in HICs
Type of pregnancy	Singleton	Twin/multiple
Outcomes	Focused on SMM outcomes or factors	1. Out of scope or not focused on SMM outcomes 2. Focused on maternal mortality outcomes 3. Focused on neonatal outcomes

Table 1:
Inclusion and exclusion criteria for screening of articles by title and abstract.

Table 3:

Reasons for Exclusion	n=
Focus on association of only one factor with SMM	9
Focus on association of socioeconomic factors with SMM	5
Focus on association of ethnic factors with SMM	2
Outcomes not reported in terms of SMM (substandard care or future progress focus)	2
Focus on model validation as outcomes	1
Focus on definitions of SMM criteria instead of which criteria to be included	1
Total Exclude	20

Inclusion and Exclusion Criteria

Table 1 summarizes the inclusion and exclusion criteria for articles to pass the initial screening by title and abstract.

Study Selection

The initial PubMed search yielded 52 results, which was condensed to 24 after filters. CINAHL produced 145 results, 105 after filters. Scopus produced 574 results, 206 after filters. This resulted in 335 papers. Results from the databases were combined using the reference manager Mendeley yielding 288 papers after duplicates were removed. Subsequent results were screened for eligibility by title and abstract according to the inclusion and exclusion criteria in Table 1. The breakdown for reasons 261 papers were excluded from the review are seen in Table 2. The remaining 27 articles underwent a full text review, of which 20 were excluded for the reasons in Table 3. Seven articles were included. To supplement the search, three articles were added from the reference list of the other articles,6-8 totalling ten articles included in the review. The flowchart in Figure 1 illustrates the selection process.

Reasons for Exclusion	n=
Studies out of scope/not focused on SMM outcomes	112
Not in HICs	71
Studies focused on maternal mortality outcomes	26
Studies focused on neonatal outcomes	10
Studies focused on twin/multiple births	2
Protocol	12
Poster/ Conference	9
Systematic Review	7
Literature Review	6
Commentary Article	4
Case Study	1
Narrative Review	1
Total Excluded	261

Table 2:
Reasons for exclusion of articles after screening by title and abstract.

Article Validity

The ten articles selected for this review were critically evaluated using the EBL Critical Appraisal Checklist.17

Results

Summary Tables

From a total of ten studies, there were six retrospective cohort studies [6,7,9,12-14], three prospective cohort studies[8,11,15], and one that had a combined type of first half retrospective and second half prospective cohort.10 The studies were conducted across eight countries, the majority in the USA [3], and one each in Canada[9], Australia[11], Ireland[8], Italy[15], Netherlands[14], United Arab Emirates[10] (this is a HIC according to World Bank). One study12 covered three countries, USA, Australia, and England. The sample sizes ranged from 19 cases of SMM (among 2,773 live births)11 to 47,973 cases of SMM (among 3,556,206 deliveries)[7]. Study periods ranged from six months[8,11] to ten years.[15] A summary of the characteristics of the included studies is presented in Table 4 in the appendix (see Box 1 in Section 2 for abbreviations used in table).

Critical Appraisal

The EBL Critical Appraisal Tool [17] was used to assess bias in studies by evaluating the validity and quality of each study reviewed in an objective and standardised manner (Appendix A). The validity scores are presented in Table 5. All articles have section and overall scores above 75% and thereby were deemed valid.

Study	Population Validity	Data Collection Validity	Study Design Validity	Results Validity	Overall Validity
Dzakpasu S, *et al.* (2020)	100%	100%	100%	100%	100%
Ghazal-Aswad S, *et al.* (2013)	100%	100%	100%	83%	96%
Jayaratnam S, *et al.* (2018)	80%	100%	100%	83%	91%
Lazariu V, *et al.* (2017)	100%	100%	100%	100%	100%
Leonard SA, *et al.* (2019)	100%	100%	100%	100%	100%
Lipkind HS, *et al.* (2019)	100%	100%	100%	83%	96%
Mhyre JM, *et al.* (2011)	100%	100%	100%	100%	100%
O'Malley EG, *et al.* (2016)	80%	100%	100%	83%	91%
Witteveen T, *et al.* (2016)	100%	100%	100%	100%	100%
Zanconato G, *et al.* (2019)	100%	100%	100%	83%	96%

Table 5:
Validity scores calculated using EBL Critical Appraisal Tool

Objective 1: Comparing SMM definitions and criteria

Six of the articles discussed SMM definitions and case criteria.[6,8,9,13-15]To identify SMM cases, two articles from the United States used the International Classification of Diseases 9th edition (ICD-9),[6,13] one Canadian article used both the ICD 10th edition (ICD-10) and the Canadian Classification of Health Interventions (CCI) [9], two European articles used the WHO maternal near miss criteria1[4,15], and one Irish article[8] used the WHO criteria alongside the Scottish Audit criteria.[16] All of these articles either commented on the use of the criteria to identify cases, or attempted to expand on the definitions/criteria of these systems.

Lazariu and colleagues expanded on the ICD-9 criteria for SMM cases by including a long hospital stay (at or above 90th percentile) and admission to the intensive care unit (ICU) as part of the definition.[6] This resulted in a 3% increase in SMM cases compared to using ICD only. Mhyre and colleagues suggested a similar expansion on the ICD-9 definition, by adding end-organ injury with length of stay greater than 99th percentile or discharge to second medical facility.[13] Dzakpasu and colleagues investigated a list of morbidity types and subtypes, their incidence and their association with case fatality and length of hospital stay.[9] They evaluated thirteen SMM types that were not a part of the ICD-10 or CCI, of which six were suggested for inclusion.

O'Malley and colleagues reported double the cases identified as SMM using the Scottish Audit criteria, compared to WHO criteria.[8]

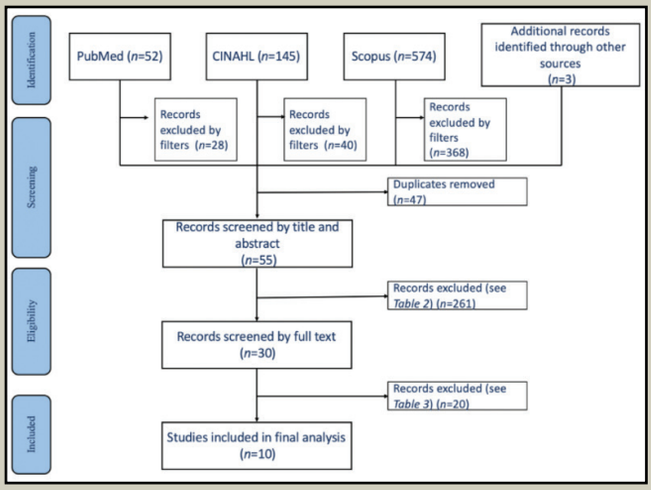


Figure 1:
PRISMA chart outlining article selection process from initial search to final inclusion

Zanconato and colleagues, and Witteveen and colleagues both investigated the 2011 WHO SMM criteria. The former focused on using only the intervention-based and organ dysfunction criteria.15 Meanwhile the latter group used all three WHO criteria categories separately and suggested that disease-based criteria identified the most cases, while organ dysfunction criteria missed about 60 percent of SMM cases.[14]

Objective 2: Main types of SMM

Seven of the articles detailed the main types

of SMM in their respective countries.[8-12,14,15] All but one[12]of these articles reported a severe obstetric haemorrhage as the main type of SMM. The Italian15, Irish8, and United Arab Emirates[10] studies reported haemorrhage and hypertensive disorders as the most common types of SMM. Meanwhile, the Canadian[9] and Dutch[14] studies reported it to be ICU admission. Other types that were common between some studies were pre-eclampsia and/or eclampsia[9,11,12], diffuse intravascular coagulation (DIC)[12,14], and hysterectomy.[9,12]

Objective 3: Principle risk factors of SMM

Six of the articles described risk factors associated with SMM.[6,7,9,12-14] The two most common risk factors were advanced maternal age[6,7,9,12,14] and a caesarean delivery.[6,7,9,15] Advanced maternal age was either defined as above age 35 or 40 depending on the study. Leonard and colleagues reported that SMM was two times higher among women with a caesarean delivery than a vaginal delivery.[7] The study also did not find an association between SMM and pre-pregnancy obesity,[7] while Lazariu and colleagues reported an association between SMM and being underweight instead.[6] Two studies identified maternal comorbidities as a risk factor, which included a variety of conditions such as pulmonary hypertension, chronic renal disease, and malignancy.[7,13] Leonard and colleagues also reported that SMM was two times higher among women with comorbidities.[7] Two studies suggested non-white origin to also be a risk factor.[6,15]

Discussion

This study looked at ten international articles to ascertain criteria used to identify SMM, and to identify the main types of and risk factors contributing to SMM among eight HICs. There is no international consensus on which criteria to use to identify SMM. As seen in the results, the ICD and the WHO are common sources of identification criteria for countries, with two additional sources being the CCI and the Scottish Audit. Two articles with long study periods and large samples suggested to expand the ICD criteria to include longer hospital stay and admission to ICU/secondary medical facility, to more comprehensibly identify SMM cases.[6,13] The Canadian study evaluated the ICD-10, CCI, and new measures to propose a master list of types and subtypes that can be used to identify SMM.[9] They suggested adding the following types of SMM to the ICD-10 list: severe pre-eclampsia, HELLP syndrome, acute fatty liver and red blood cell transfusion, ICU admission, and inversion of uterus.[9] This study had a large, diverse sample allowing external validity, is recent (2019), demonstrates extensive research, clarity, and used a multidisciplinary team to limit bias. According to the WHO, the organ dysfunction criteria are the most promising markers to detect SMM.[14] However, as demonstrated by Witteveen and colleagues (and seen to an extent in O'Malley and colleagues8), these criteria missed 60% of cases, and instead disease-based criteria warrant further attention.[14] Thereby, these findings provide guidance on how to achieve a representative definition of SMM. Specifically, the route of using disease-based criteria, as well as the measures identified by the Canadian study should be used as the basis for future identification of SMM.

As HICs use different criteria to identify SMM cases and consist of a differing composition of individuals, the main types and risk factors of SMM were compared between countries. Much similarity was nevertheless seen between the principal types and risk factors affecting women in the different HICs. This suggests a few common factors that need to be addressed and monitored to limit SMM in the future. The most common types of SMM were severe haemorrhage as identified by six articles[8-11,14,15], hypertensive disorders named by three articles[8,10,15], and pre-eclampsia/eclampsia also by three.[9,11,12] Of these articles, O'Malley and colleagues is of a lower quality mainly due to the small sample size and limitation to the HDU, which

reduces external validity and the ability to draw generalisable conclusions.8 However, it remains in agreement with the other articles on principal types of SMM.
The most common risk factors between countries were advanced maternal age[6,7,9,12,14] and caesarean delivery[6,7,9,15], with two studies also suggesting comorbidities as a factor.[7,13] An issue that arose was the differing definition of advanced maternal age, as it was either above 35 or above 40 years. It is important to establish a consensus for this factor for improved study comparability and clinical case screening. The association of the factors with SMM was identified in previous literature[5,18], with the addition of obesity as a factor. However, Leonard and colleagues did not find this association[7] and being underweight was suggested as a factor instead[6]. The role of pre-pregnancy weight in SMM requires further study. Two studies also suggested race to be a risk factor, specifically non-white origin[6,15]. One study was from New York State[6], using a very large, diverse sample, and the other was Italian[15], using a sample of just over 100 SMM cases at a single institution (lacking external validity). However, racial disparity was also documented in two other studies, which reported increased SMM among non-western immigrant women[19] or sub-Saharan African women[20]. The role of race should also be further investigated as a risk factor, and to determine if this is a consistent finding among various countries or if it is a bias due to the confounding socioeconomic status.

Strengths and Limitations

A strength of this literature review is the inclusion of a variety of international articles representing eight HICs, most of which have large sample sizes, and all of which were critically appraised to be over 90% valid. Furthermore, using three databases provided access to over 700 studies, and the systematic approach allowed reproducibility.
Limitations include being limited to only ten articles and 8 HIC due to word restrictions, only one researcher screened the articles, and inclusion was limited to free full texts in English, as additional studies were of interest but were not accessible. Additionally, two of the included studies, despite having over 90% validity, had small numbers of SMM cases[8,11].

Conclusion

SMM is an important measure of maternal quality of care and yet there is no international consensus on which criteria to use to identify SMM. This literature review sought to bridge this gap and was able to identify disease-based criteria and the Canadian study criteria as promising measures of SMM. Despite the differences in criteria used between HICs, similar principal types of SMM were identified: severe haemorrhage, hypertensive disorders, and pre-eclampsia/eclampsia. Furthermore, common risk factors were also identified among the countries (advanced maternal age and caesarean delivery) that can assist with screening and identifying potential cases at risk of SMM. A consensus on defining SMM should be reached to allow obstetricians to identify patients that are at risk of SMM and to practice improved preventative medicine.

Future Investigations

As disease-based criteria and the Canadian study criteria seem to provide a more comprehensive insight into SMM than other methods. These measures should be further studied in other HICs to determine how they compare with previous sources of criteria. Additionally, future investigation into the association of risk factors with SMM, particularly weight and race, is required to improve early screening for SMM cases.

Acknowledgements

I would like to acknowledge the literature review supervisor Dr Richard Greene, from the Obstetrics and Gynaecology department at Cork University Maternity Hospital.

Appendix A

EBL Critical Appraisal Checklist[17]		Dzakpasu S, *et al.* (2020)	Ghazal-Aswad S, *et al.* (2013)	Jayaratnam S, *et al.* (2018)	Lazariu V, *et al.* (2017)	Leonard SA, *et al.* (2019)	Lipkind HS, *et al.* (2019)	Mhyre JM, *et al.* (2011)	O'Malley EG, *et al.* (2016)	Wittveen T, *et al.* (2016)	Zanconato G, *et al.* (2019)
Section A: Population	Is the study population representative of all users who might be included in the study?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Are inclusion and exclusion criteria clearly outlined?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Is the sample size large enough to obtain precise estimates?	Y	Y	N	Y	Y	Y	Y	N	Y	Y
	Is the response rate sufficient for precise estimates?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Is the choice of population free from bias?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	If a comparative study: Were participants randomized?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	At baseline, were the groups comparable?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	If not, was this addressed in the analysis?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Was there informed consent?	N/A	Y	Y	N/A	N/A	N/A	N/A	Y	Y	Y
Section B: Data Collection	Are data collection methods reported clearly?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	If a face-to-face survey, were inter-observer and intra-observer bias reduced?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Is the data collection instrument validated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	If based on commonly obtained statistics, are they free from subjectivity?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Is the outcome measured at an appropriate time for reporting the intervention's effect?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Is the instrument included in the publication?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Are questions presented sufficiently clear in order to obtain accurate answers?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Were those involved in data collection not involved in supplying a service to the target population?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Section C: Study Design	Is the study type / methodology operated appropriate?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Is there face validity?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Is the research methodology precisely reported at a level that would permit its replication?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Was ethical approval granted?	N/A	Y	Y	N/A	N/A	N/A	N/A	Y	Y	Y
	Are the outcomes clearly reported and discussed regarding the data collection?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Section D: Results	Are all the results clearly reported?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Are confounding variables accounted for?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Do the conclusions reflect the analysis accurately?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Is subset analysis a minor, rather than a major, focus of the article?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Are suggestions provided for further areas to research?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Is the study externally valid?	Y	N	N	Y	Y	U	Y	N	Y	N

Legend: Yes (Y), No (N), Unclear (U), Not Applicable (N/A); Y/Total = %

Appendix B

Author (Year), Location, *Title*	Objectives	Study Type, Study population, Sample size	Study Methodology	Key Findings	Strengths & Limitations	Future Research
Dzakpasu S, *et al.* (2020) Canada (Excluding Quebec) *Severe maternal morbidity surveillance: Monitoring pregnant women at high risk for prolonged hospitalisation and death.* (9)	1. To propose a comprehensive definition of SMM 2. To create an empirically justified list of SMM types and subtypes 3. To use information in 1 & 2 to examine SMM in Canada.	Retrospective cohort All hospital deliveries in Canada (excluding Quebec) between 2012 and 2016 n = 22,799 cases of SMM (among 1,418,545 deliveries)	Discharge Abstract Database of the Canadian Institute for Health Information was used to obtain: • maternal/infant characteristics • labour & delivery • diagnoses & procedures SMM cases were identified using ICD-10 and CCI Potential SMM types and subtypes were evaluated by examining rates, temporal trends, length of hospital stay, and case fatality rates for 2006-2015. The list of SMM was then used to describe SMM in Canada for 2012-2016.	1. SMM rate was 16.1/1000 deliveries 2. Main types of SMM were severe pre-eclampsia and HELLP syndrome, severe postpartum haemorrhage, maternal ICU admission, and hysterectomy. 3. SMM rate was higher in older women (>40yo), and previous or current caesarean delivery. 4. Twelve SMM types were identified and 46 subtypes.	Strengths: • Very large sample size • Included ~98% of all deliveries in Canada • Multidisciplinary input and evidentiary support from contemporary data • The hospitalisation data source has made coding changes to facilitate comprehensive monitoring • Proposed new criteria for SMM • Long study period Limitations: • Inability to identify some clinically relevant cases due to data source coding (severe obesity) and to distinguish between pre-existing and acute complications • Exclusion of Quebec	To include Quebec, and use a more detailed data source which can monitor a wider range of case types
Ghazal-Aswad S, *et al.* (2013) United Arab Emirates (Abu Dhabi emirate) *Severe Acute Maternal Morbidity in a High-Income Developing Multiethnic Country.* (10)	To study the epidemiology of SMM in a HIC.	Retrospective cohort first 3 years and prospective cohort last 3 years All births occurring in maternal units with over 500 births/year (4 units) in the Emirate of Abu Dhabi between 1998 and 2003. n = 926 cases of SMM (among 122,705 deliveries)	Clinical criteria consisting of eight conditions were used to identify SMM cases. First 3 years, cases obtained from hospital records. Last 3 years, cases obtained using form with relevant clinical data.	1. SMM rate was 7.5/1000 deliveries 2. The most common types of SMM were hypertensive disorders and haemorrhage.	Strengths: • Long study period • Prospective design portion • Clinical criteria was clearly defined Limitations: • Old dataset • Only one province was included and limited to large maternity units	Inclusion of a wider range of clinical, intervention, and disease-based criteria to identify SMM cases.
Jayaratnam S, *et al.* (2018) Australia *Maternal 'near miss' collection at an Australian tertiary maternity hospital.* (11)	To determine the rate and aetiology of maternal near misses at KEMH using WHO near miss criteria.	Prospective observational All women admitted to KEMH between December 1 2014 and May 31 2015 during pregnancy or within 42 days of its termination n = 19 cases of SMM (among 2,773 live births)	A form with clinical and biochemical parameters was used to identify potential cases based on WHO criteria of near misses Cases were identified and collected daily; a structured form was then completed when case was confirmed to be SMM (including age, length of hospital stay)	1. SMM rate was 7/1000 deliveries 2. Main types of SMM were post-partum haemorrhage, pre-eclampsia, and early pregnancy complications.	Strengths: • Cases were reviewed independently by two investigators • Prospective design Limitations: • Small sample • Only one hospital; not nationally representative • Short study period	Developing software that can automatically identify near miss cases using routinely collected information Longer study period Expanding to multiple hospitals across the country
Lazariu V, *et al.* (2017) United States (New York) *Severe maternal morbidity: A population based study of an expanded measure and associated factors.* (6)	1. To evaluate the impact of expanding the CDC measures of SMM to include pre-existing conditions and ICU admission. 2. To identify risk factors associated with SMM.	Retrospective population-based observational study All New York State female residents, 10-55yo, who had live births at New York acute care hospitals between 2008 and 2013 inclusive n = 34,478 cases of SMM (among 1,352,600 hospital deliveries)	Information was collected from administrative database records (hospital discharge, vital records) SMM cases were identified using the 9th edition of ICD (ICD-9 CM), with the addition of long hospital stay (at or above 90th percentile) and admission to ICU.	1. Case incidence of 2.55% (25.5/1000) using the expanded criteria (3% increase in cases compared to using ICD only) 2. Risk factors for SMM were identified as age<20 or >35, underweight, caesarean delivery, non-white race.	Strengths: • Very large sample size (including 93% of live birth records for New York State) • Expanded the ICD definition of SMM • Long study period Limitations: • Hospital discharge records were used, not all complete, and accuracy can vary by hospital • Pre-pregnancy comorbidities were not recorded consistently in database	Can expand the study to other States Further research into pre-pregnancy comorbidity

Systemic Reviews

Author (Year), Location, *Title*	Objectives	Study Type, Study population, Sample size	Study Methodology	Key Findings	Strengths & Limitations	Future Research
Leonard SA, *et al.* (2019) United States (California) *The contribution of maternal characteristics and cesarean delivery to an increasing trend of severe maternal morbidity.* (7)	To evaluate the association of advanced maternal age (≥35yo), pre-pregnancy obesity BMI ≥30kg/m^2), pre-pregnancy comorbidities, and caesarean delivery with SMM.	Retrospective population-based cohort study Live births in California between January 1 2007 and December 31 2014, with gestation >20 weeks n = 47,973 cases of SMM (among 3,556,206 deliveries)	Used linked birth record and patient discharge data from live births SMM cases were identified using the ICD-9-CM Multivariable logistic regression model used to assess association	1. SMM rate was 13.5/1000 deliveries 2. Pre-pregnancy comorbidities and caesarean delivery were associated with SMM (two-fold higher), advanced age was associated to a lesser degree, but pre-pregnancy obesity was not associate.	Strengths: • Very large, diverse sample size • Linkage between vital records and patient records allowed the study of pre-pregnancy risk factors • Long study period Limitations: • Observational study • Data may lead to misclassification (pre-pregnancy weight was self-reported) • Limited to California • Included limited number of risk factors	Expand to other States Include additional risk factors
Lipkind HS, *et al.* (2019) USA, Australia, England *Severe maternal morbidity during delivery hospitalisation in a large international administrative database, 2008–2013: a retrospective cohort.* (12)	To identify pregnancy complications and associated risk factors leading to SMM	Retrospective cohort Delivery hospitalisations in large university hospitals in USA, Australia and England between 2008 and 2013 n = 4,333 cases of SMM (among 516,781 deliveries across 18 hospitals)	Dr. Foster Global Comparators Database was used to identify delivery hospitalisations with life-threatening diagnoses or use of life-saving procedures SMM cases were identified using the ICD-10 in England and Australia and ICD-9 CM in the USA Frequency per country was calculated.	1. Overall SMM rate was 8.2/1000 deliveries: • 15.6 in USA • 8.2 in Australia • 5.0 in England 2. Most common types of SMM were DIC, acute renal failure, cardiac events ventilation, hysterectomy, and eclampsia. 3. Risk factors associated with SMM were advanced maternal age (>40yo), hypertension, diabetes, and substance abuse.	Strengths: • Large, international sample size • Use of academic medical centres for consistency • Long study period Limitations: • Data relies on hospital discharge coding, which can vary between countries and hospitals • Limited number of hospitals are represented, with more than half (57%) from England – countries are not equally represented • May not be representative of country as only academic centres included	Inclusion of more hospitals across the countries for better generalization Equal representation of countries to improve comparability
Mhyre JM, *et al.* (2011) United States *Influence of Patient Comorbidities on the Risk of Near-miss Maternal Morbidity or Mortality.* (13)	To determine the extent to which it is possible to predict which patients will experience SMM (to identify risk factors for SMM).	Retrospective cohort Maternal hospital admissions for delivery in the Nationwide Inpatient Sample (NIS) between 2003 and 2006 n = 4,550 cases of SMM (among 3,463,327 deliveries)	NIS dataset was used (which is a 20% stratified sample with ~1000 hospitals) SMM cases were identified using ICD-9-CM	1. Defined SMM (in addition to ICD measures) as end-organ injury with length of stay greater than 99th percentile or discharge to second medical facility. 2. SMM rate was 1.3/1000 deliveries 3. The risk factors contributing to majority of SMM were comorbidities (pulmonary hypertension, malignancy, SLE) and complications (DIC, acute liver disease, acute respiratory distress syndrome).	Strengths: • Large, diverse, national sample size • Expanded on the ICD-9 definition of SMM • Access to pre-existing comorbidity data Limitations: • Specific ICD codes do not exist for many conditions (placenta accreta), so they could not be studied • NIS does not have enough sample size to study rare conditions • Old dataset	Investigate hospital-level variation in SMM Investigate the impact of using other measures (besides ICD-9) to identify SMM cases on sample
O'Malley EG, *et al.* (2016) Ireland *Maternal near miss: what lies beneath?* (8)	1. To determine incidence and common reasons for admission to high dependency unit (HDU) 2. To determine categories (types) of SMM	Prospective cohort All women admitted to the Coombe Women and Infants University Hospital (CWIUH) HDU from May 5 to November 5 2014 n = 128 admissions to HDU (among 4,502 live births)	Study population was identified prospectively and data was recorded including demographics, admission reason, length of stay, interventions, ICU transfer, and outcomes. Scottish Audit and WHO criteria were used to identify SMM cases Sample was divided into three groups: 1) near miss cases 2) severe maternal complications but no organ dysfunction 3) not SMM	1. Of the 128 admissions to HDU, 16 women fulfilled SMM criteria defined by the Scottish Audit, while 8 met the WHO criteria; 83 women with severe maternal complications. 2. Common reasons for admission to HDU were haemorrhage, hypertension, and sepsis.	Strengths: • Used two different SMM criteria to identify cases (Scottish Audit and WHO) • More recent dataset Limitations: • Short study period • Small sample number (16+8 cases meeting criteria) • Limited to HDU admissions; may be missing cases of SMM	Expand study to other hospitals in the country for better representation Increase study period to obtain greater sample size

Author (Year), Location, *Title*	Objectives	Study Type, Study population, Sample size	Study Methodology	Key Findings	Strengths & Limitations	Future Research
Witteveen T, *et al.* (2016) Netherlands *Validating the WHO Maternal Near Miss Tool in a high-income country.* (14)	1. To investigate the applicability of the WHO maternal near miss tool (MNM tool) in Netherlands. 2. To determine if organ dysfunction criteria (from MNM tool) are suitable markers of SMM.	Retrospective cohort Women with SMM in Netherlands between August 1, 2004 and August 1 2006. n = 2,552 cases of SMM (among 371,623 deliveries)	MNM tool was applied to data collected in a previous prospective study (LEMMoN study)	1. About 9% of cases identified as SMM in the LEMMoN study were missed using the WHO criteria. 2. Organ dysfunction criteria failed to identify ~60% of SMM cases. Disease-based criteria detected ~90% of SMM cases. 3. The most common types of SMM were postpartum haemorrhage, DIC, and admission to ICU. 4. Risk factors associated with SMM were identified as higher maternal age (35+) and long hospital stay.	Strengths: • Two independent investigators applied MNM tool to cases and discrepancies were discussed with team • Large sample size Limitations: • Used data from previous study that identified cases based on other criteria • Incomplete or missing information in the database (bias limited by team discussion) • Older dataset	Applying MNM tool on more recent dataset, with an emphasis on disease-based criteria as opposed to organ dysfunction criteria
Zanconato G, *et al.* (2019) Italy *Perinatal outcome of severe obstetric complications: findings of a 10-year hospital-based surveillance study in Italy.* (15)	To determine the incidence and clinical patterns of SMM in Italy.	Observational prospective study Women admitted to the University Hospital of Verona between January 2007 and December 2016 n = 151 cases of SMM (among 17,560 deliveries)	Medical records in the obstetric ward and ICU provided the data which was entered into an Access database SMM cases were identified using the 2011 WHO criteria (specifically the intervention-based and organ dysfunction criteria)	1. SMM incidence rate was 8.6/1000 deliveries 2. The most common types of SMM were severe obstetric haemorrhage and hypertensive disorders. 3. Factors also associated with SMM were pre-term birth, caesarean section, and sub-Saharan African origin.	Strengths: • Long study period • Prospective design Limitations: • Single institution • Only intervention-based and organ dysfunction criteria were used to identify cases; may be missing SMM cases	Include disease-based WHO criteria to identify SMM cases.

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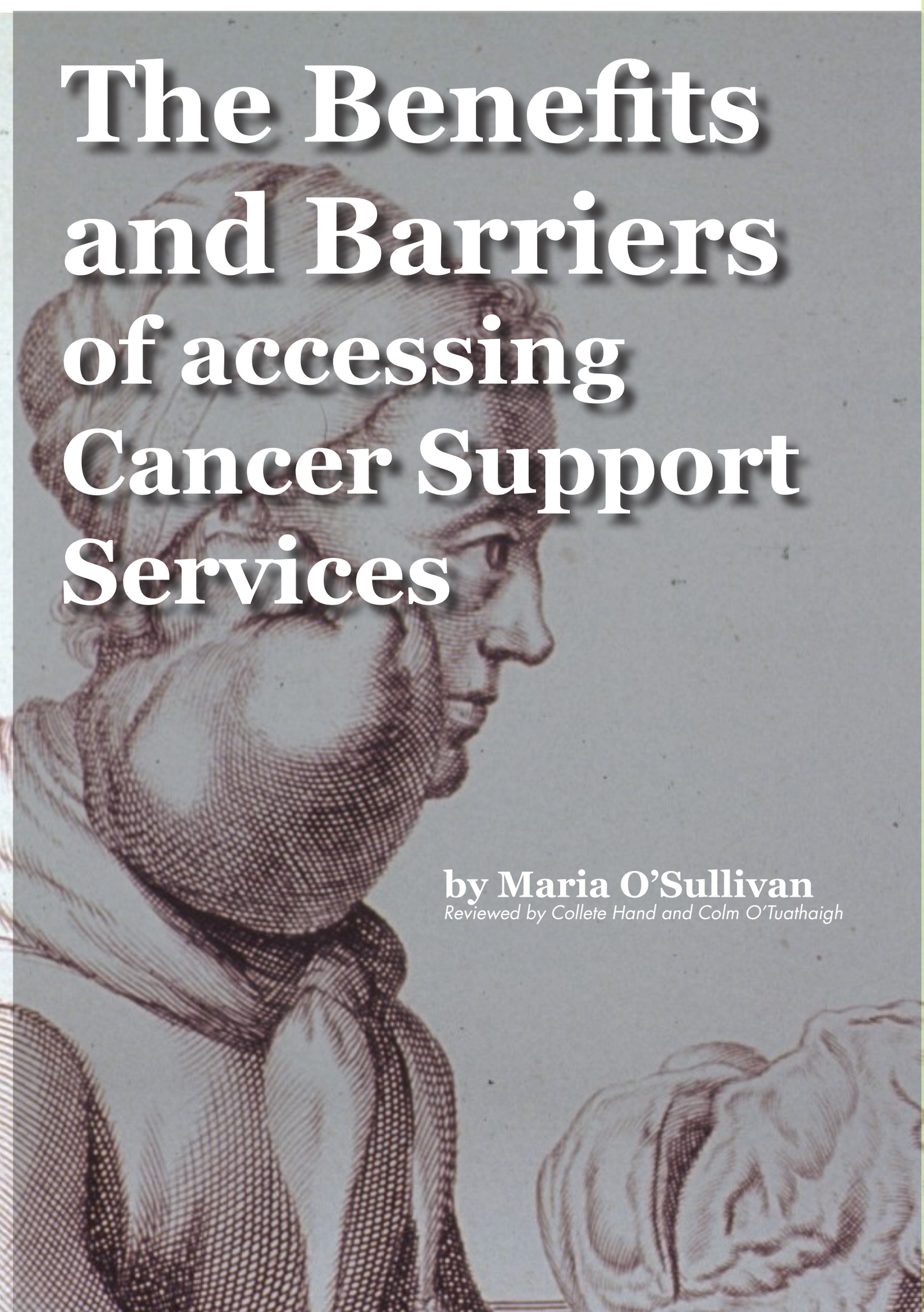
The Benefits and Barriers of accessing Cancer Support Services



by Maria O'Sullivan
Reviewed by Collete Hand and Colm O'Tuathaigh

Abstract

Introduction

Cancer is a substantial cause of morbidity and mortality worldwide. In Ireland, rising cancer incidence means that the burden on society will continue to increase. Recent recognition of the large impact of psychological distress on patients with cancer has led to suggestions to use support centres to mitigate this distress. Thus, the benefits of participation and barriers to attendance must be explored.

Aims & Objectives

To systematically review scientific literature and determine the:
(i) Sociodemographic composition of cancer support centres.
(ii) Benefits of support services to patients with cancer.
(iii) Barriers/facilitators to support centre attendance.

Methods

Electronic searches were carried out PubMed and the Cumulative Index to Nursing and Allied Health Literature (CINHAL) databases using key words addressing the research question. Ten articles were selected and critically appraised.

Results

A summary of article results showed that while various groups remain underrepresented in support centres, new evidence suggests this may be changing. Increased support service attendance was linked to greater benefits. No change in anxiety or depression with attendance were seen. Barriers to attendance were identified.

Conclusions

The literature showed benefits to support services, but long term benefits must be further investigated. Future research quantitatively assessing benefits of support services, using validated assessment instruments are necessary. Psychological benefits of participation are still unclear. Validated questionnaires to assess the barriers to attendance must be developed. Lastly, there is a lack of studies on the benefits of and barriers to support services participation in the Irish population.

Introduction

Cancer is a leading cause of death and disability worldwide, accounting for almost 1 in 6 deaths [1]. In Ireland, cancer was the second most common cause of death [2]. The number of Irish cancer cases will rise by 84% for females and 107% for males between 2010 and 2040 [3]. Thus, cancer will remain a national and global health priority. Psychological distress is commonly experienced by patients with cancer. This distress may manifest at various stages [4-7]. Curative cancer treatment may not meet the needs of patients completely, particularly their psychological needs. Previous studies have assessed the unmet needs of patients with cancer [8-10]. In Ireland, the National Cancer Strategy 2017-2026 deems psycho-social support as ''essential" in the care of cancer patients and survivors [11]. The National Institute for Health and Care Excellence (NICE) guidelines on' Improving supportive and palliative care for adults with cancer' recommends support groups as a resource for patients with cancer [12].

Objectives

The objective of this systematic review is to evaluate the published literature from scientific databases to determine the:

i. Typical sociodemographic composition of cancer support centres, including underrepresented groups.
ii. Benefit of support services in patients with cancer.
iii. Barriers/facilitators to cancer support service participation.

Methods

Electronic searches were performed on the PubMed and CINAHL databases to attain literature corresponding to the research objectives.

1. **Two articles were recommended by my project supervisor**:

They pertained to two randomised control trials (RCT) looking at the benefits of support group interventions and were identified on the PubMed database [13, 14].

2. **Forty-five articles were selected on PubMed using the following search equation:**

(((Support group[Title]) AND Cancer [Title]) AND participation[Title]) OR ((Cancer support group*[Title]) AND benefit*)

Filters were added to the search: Articles since 2005 (reduction to 30 articles) and adults aged 19+ years (reduction to 22 articles).

The remaining articles were manually reviewed by reading titles and abstracts based on selection criteria. Main reasons for exclusion were the article focusing on:

i. Health professional/specialist/carer/group leaders' opinions on support groups
ii. Support group cost comparisons
iii. 'Lurkers' (i.e. users not actively participating) in online support groups.
iv. Specific minority group.

Next, any articles meeting the selection criteria without free full text available (18 articles) were excluded. Four PubMed articles were selected.

3. **67 articles were selected on CINAHL using the following search equation:**

((TI Cancer support group*) AND (benefit)) OR ((TI Support group) AND (TI Cancer) AND (TI participation))
The same time period filter was applied (i.e. articles since 2005) with 46 results. The filter 'All Adults' brought the article total to 24.

17 were duplicates of articles from PubMed. Also excluded were articles focusing on: Spouse/siblings/parents

Articles without full free text available were removed after selection criteria application. Three CINAHL articles were selected.
Figure 1 and 2 show schematics of article selection from PubMed and CINAHL databases.

4. **One article identified from screening reference section of other articles selected:**

This was a longitudinal, cross-sectional study on barriers to support group attendance [15]

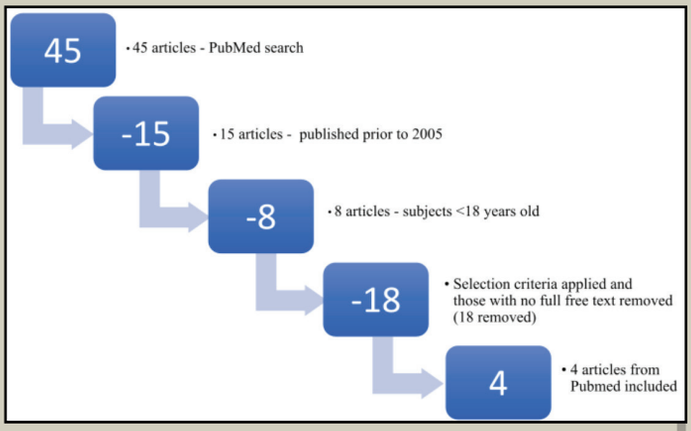


Figure 1:
Flow-chart depicting study selection for PubMed data-

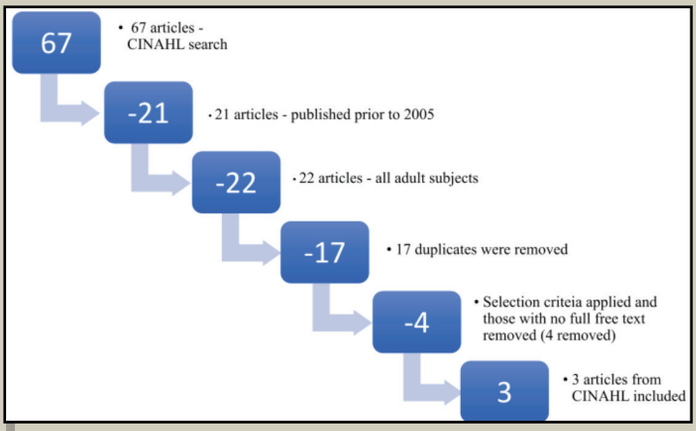


Figure 2:
Flow-chart depicting study selection for CINAHL data-

Selection crtiteria

See table 1. Ten remaining articles were summarised under the headings: objective, study type, methods, sample size, study population and selection criteria, key findings and strengths/limitations (Table 2). They were critically appraised using the Evidence-based librarianship (EBL) critical appraisal checklist tool. Validity scores were

determined (Table 3) {L., 2006 #243}[16].

Results

3.1 Result Summaries

Table 2 summarises article results. Box 1 demonstrates abbreviations used in Table 2.

3.2 Quality of studies

The EBL critical appraisal checklist tool was employed to compute section and overall validity scores. Table 3 section validity scores were calculated using the formula:
Validity Score = (Y) ÷ (Y + N +U). The overall validity score, was an average of the four section validity scores. Scores ≥75% imply validity.
Table 3: Section and Overall Validity Scores as calculated using the EBL Critical Appraisal Checklist

3.3 Sociodemographic composition of support groups

3.3.1 Overrepresented groups

Four cross-sectional studies assessed support group composition. Overrepresented parties, included those that are; young [22, 23], white/

Inclusion criteria:	Exclusion criteria:
- ≥18 years old	- <18 years old
- Articles in English	- Articles not in English
- Patients with cancer and cancer survivors	- Health professionals/specialists opinions on support services
- Studies after 2005	- Studies regarding support centre leaders
- Benefits of cancer support services	- Cost comparison for support service types
- Barriers to participation in cancer support services	- Studies involving family carers/caregivers/ spouses
- Sociodemographic composition of support services	- Studies regarding physical activity in patients with cancer
	- Studies looking at lurking in online cancer support services
	- Studies with primary focus on a certain ethnic/minority group

Table 1:
Selection Criteria

RCT	Randomised control trial
Non-RCT	Non-randomised control trial
QOL	Quality of life
HADS	Hospital Anxiety and Depression Scale
CRI	Coping Resources Inventory
FQ	Fatigue Questionnaire
Hx.	History

Box 1:
Abbreviations used in Table 2.

Caucasian [20, 21], female [20, 22], have a higher education level [21-23], higher income, are married, are employed [23], and those with breast cancer/multiple myeloma [21].

3.3.2 Underrepresented groups

A 2010 UK cross-sectional study [20], showed increased attendance in males/those of lower socioeconomic status, compared to previous studies [22].

3.4 Benefits of support groups participation

Eight studies assessed the benefits of support group attendance for patients with cancer.

3.4.1 Attendance Frequency

Two cross-sectional studies showed a positive correlation between attendance levels and level of perceived benefit [20, 21]. A longitudinal study showed that emotional well-being was related both to coping style and frequency of support group use. Frequent participation, particularly helped those approaching their emotions less actively [13].

3.4.2 Anxiety and depression

Two studies, one RCT and one non-RCT, showed no significant change in anxiety and depression, using the Hospital Anxiety and Depression Scale (HADS) [18, 19]. Similarly, a randomised longitudinal study, using the Center for Epidemiological Studies-Depression (CES-D) survey, showed no variation in depressive symptoms [17].

3.4.3 Health-related quality of life

A RCT showed that, health related quality of life was positively associated with the support group intervention [19]. Conversely, a descriptive cross-sectional study showed an increased health-related quality of life to be insignificant [23].

3.4.4. Quality of life

A RCT measuring quality of life showed a positive correlation with increased quality of life in the intervention group and negative correlation in the control group at 6 weeks [14]. This change returned to baseline at the study completion.

3.4.5. Other Benefits

i. Perceived psychological benefits greater in females than males [20].
ii. Decreased fatigue was positively associated with support group intervention [19].
iii. The moderated group was associated with increased participation when compared to the peer-led group [17].
iv. Support group intervention was positively associated with increased coping resources [18].

3.5 Barriers/ Facilitators to support group

participation

3.5.1 Barriers:

Two studies examined barriers to support group attendance for patients with cancer.

A longitudinal study of drop-outs and cross-sectional study of non-attendees showed that barriers differed between both groups [15]. It identified two different reactions in support groups drop-outs (i.e. positive or negative attitude towards support groups). Those with different attitudes had different reasons for drop-out.
A cross-sectional study looking at barriers to support group attendance cited similar reasons to those cited by Ussher et al [15], including geographical location and lack of awareness of support group existence [21].

3.5.2 Facilitators:

Two studies looked at the facilitators of support group attendance for patients with cancer.

3.5.1.1 Common facilitators

i. Facilitators included patients having family/ friends encourage or support their attendance [21, 22].

3.5.2.2 Other facilitators

i. Patients perception of support group benefit, actively coping, and having an insufficient support system for the patients' needs [22].
ii. Increased disease severity/stress due to illness [21].

Discussion

Table 2 details strengths and weaknesses of each study.

4.1 Sociodemographic composition of support groups

A 2011 cross-sectional study of the UK population contradicted results of similar previous studies. It showed an increased proportion of men/those of lower socioeconomic among attendees [20]. The authors hypothesised that this change in support groups composition may be due to new NICE guidelines introduced in 2004 [12]. Low response rate (29%), was a weaknesses of this study, which even in a large population, may affect validity. Despite support group composition appearing to change in recent studies, some sociodemographic groups remain underrepresented (e.g. males, minorities, low socioeconomic status). [20] This issue must be addressed to allow equally oppor-

Article	Population Validity Score (%)	Data collection Validity Score (%)	Study design Validity Score (%)	Results Validity Score (%)	Overall Validity Score (%)
Batenburg A. et al. (2014) [13]	0*	83	100	80	**66***
Osei D.K. et al. (2013) [14]	56*	100	100	67*	**81**
Klemm P. (2012) [17]	29*	83	100	80	**73***
Emilsson S. et al. (2012) [18]	71*	100	100	80	**88**
Björneklett H.G. (2012) [19]	78	83	100	67*	**82**
Stevinson C. et al. (2011) [20]	67*	80	100	80	**77**
Sherman A.C. et al. (2008) [21]	67*	80	80	80	**77**
Ussher J.M. et al. (2008) [15]	17*	50*	100	80	**62***
Grande G.E. et al. (2006) [22]	83	67*	100	80	**83**
Michalec B. (2006) [23]	67*	60*	80	100	**77**

***Not valid**

Table 3:
Section and Overall Validity Scores as calculated using the EBL Critical Appraisal Checklist

tunities for all patients with cancer in accessing optimum care.
Many studies focused on females and certain cancer types predominantly [13, 14, 18, 19]. These study results are not generalisable. Future studies should discern the benefits in a population with different cancer types and socioeconomic status. No studies have been carried out on the benefits of or barriers to support group participation in Ireland.

4.2 Benefits of support groups participation

Lack of consistent use of the same validated questionnaires in the seven studies makes comparison and generalisability difficult. Only five of the seven articles have validity in all four categories. Thus, study quality must be considered when reaching conclusions from the results.
Two studies showed increased perceived benefits with increased attendance. This implies that encouraging patients to attend frequently is important to obtain greater benefits [20, 21]. Study strengths include a large sample size, weaknesses include cross-sectional design, therefore no causal relationship can be established, and confounders (recall and non-response bias). The studies were valid (overall validity of 82% and 77% respectively). Benefits from attendance varied on an individual basis, depending on coping mechanisms and support systems [13]. This is important as some people may benefit more than others (e.g. people lacking a support system may benefit more). These people should be particularly encouraged to attend. Strengths of this study include its longitudinal study design; thus, causation may be established. Weaknesses include selection bias and unreported drop-out rate. This study was not valid (overall validity: 66%).
Support group attendance was shown to have no impact on anxiety and depression in patients with cancer. Two studies used the HADS to measures anxiety and depression [18, 19]. The third used the CES-D to measure depression only [17]. The use of different instruments making comparisons between the studies more difficult. Weaknesses of these studies included variation between the two groups (study vs. control or peer-led vs. moderated) either initially or during long-term follow, loss to follow up and small sample size [17, 18]; affecting external validity. The studies using the HADS were both valid. The third study was not valid (overall validity: 73%). Despite these results, it is important to examine psychological well-being in a broader context than just anxiety and depression. It is well documented that psychological needs are common in people with cancer [8-10]. Anxiety and depression don't encompass all elements of psychological needs.
Osei et al conducted the first RCT to look at online support services in patients with prostate cancer [14]. It suggested the intervention may be helpful short term (<6 weeks), increasing patient's quality of life. Weaknesses of the study include a low response rate, lack of external validity (population not diverse and recruitment from a cancer registry only); resulting in selection bias. In addition, the inclusion criteria for age didn't match the population used. It is unclear if all questionnaires used were validated. Overall validity was 81%.
Results on the impact of support groups on health related quality of life were contradictory. A RCT showed that, health-related quality of life was positively associated with the support group attendance [19]. However, a descriptive cross-sectional study [23], shows no significant increase in health-related quality of life after attendance. As the first study is a RCT with a large sample size, its results were more convincing. Both studies were valid [19, 23].
A weakness of the studies was that many don't account for the use of other support resources by participants. This could be a confounding factor in terms of the benefits they receive from the support group. In addition, there is a lack of studies looking at long term effects of support group participation. These studies showed numerous benefits, but more studies must be done to investigate the quantitative benefits using the same validated instrument in different populations to attain external validity. These studies used populations with different cancer types, therefore the results cannot be easily compared.

4.3 Barriers/ Facilitators to support group participation

A lack of awareness regarding support groups exist [15, 21]. More must be done to educate patients and families about the services available. Practical barriers were addressed in both articles. They include scheduling conflicts and geographi-

cal location (may be addressed via online support groups).
Both studies found that encouragement from friends and family was a major facilitator of attendance. Education to ensure their support in the patients decision to attend support services is therefore important [21, 22].
Weaknesses of the studies included the lack of validated questionnaires, cross-sectional design meaning no causality could be established, recall bias not being controlled for and neither study being externally valid. Two studies were valid [21, 22], one was not [15].

4.4 Limitations

Only 10 articles were evaluated in this systematic review. Only one examined the long-term effect of support groups. Validity scores were not recalculated by another reviewer. Studies were predominantly non-randomised. Studies with primary focus on a certain ethnic/minority group and papers without full free text available were excluded, this may affect the generalisability of the results.

Conclusion

Evidence suggests that support services are an important and under-utilised resource, with various benefits for people with cancer. However, patients still encounter many barriers in accessing these services. Study weaknesses included a lack of clear selection criteria and external validity; which limited result generalisability. Different instruments, parameters, study types and populations were used to measure study outcomes. The development of a validated questionnaire would allow easier result comparisons. Three studies lacked total validity. Thus, while current research shows that support groups are beneficial, weaknesses in the studies have affected the quality of the evidence. RCT using validated questionnaires would provide quantitative data and better evidence. Further research could include looking at support service benefits or barriers in an Irish population and the psychological benefits of support services.

Acknowledgments

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Table 2: Results Summary

Author (Date) / Title /Location	Objectives	Study type/ Methods	Sample size/ Study population/ Selection Criteria
Batenburg A. et al. (2014) [13] *''Emotional approach coping and the effects of online peer-led support group participation among patients with breast cancer: a longitudinal study''* The Netherlands	To investigate: The interaction between frequency of online support group participation and coping type and its impact on psychological well-being.	**Study type**: Longitudinal study **Method:** Study population completed questionnaires (t0, t1=6 months) assessing: • Participation levels. • Individual's emotional approach's to coping. • Psychological well-being.	**Sample size**: 133 **Study population:** Dutch patients with breast cancer using online support. **Inclusion Criteria:** • Website in Dutch • 24-hour discussion board • Active message board **Exclusion Criteria:** None given
Osei D.K. et al. (2013) [14] *'' Effects of an Online Support Group For Prostate Cancer Survivors: A Randomized Trial''* USA	To investigate: Whether use of an online support group increases the quality of life as perceived by patients with prostate cancer diagnosed in the past five years.	**Study type:** RCT **Methods:** • Population assigned randomly to intervention (online support) or control group (resource kits).	**Sample size:** 40 **Study population**: Men with prostate cancer diagnosed in last 5 year, aged 53-87 years. **Inclusion Criteria:** • Prostate cancer diagnosis within last 5 years • English literacy • Internet accessibility + email • Aged 40-85 years old • Married/living with partner **Exclusion Criteria:** • Prior participants of online support groups
Klemm P. (2012) [17] *''Effects of an online support group format (Moderated vs Peer-Led) on Depressive Symptoms and Extent of participation in women with breast cancer''* USA	To investigate if: Women with breast cancer will manifest less depressive symptoms if they participate in moderated online support groups versus peer-led support groups. Women with breast cancer participating in moderated online support groups will be more involved.	**Study type**: Randomised longitudinal study **Method:** Subjects randomised into 2 online support groups: • Moderated • Peer-led Intervention = 12 weeks Questionnaires: Demographics and outcome measures. Questionnaires completed: Before participation + at 6, 12 and 16 weeks.	**Sample size:** 50 **Study population:** Women with breast cancer, ≥21 years old, internet connection, English literacy, finished treatment within 32 months prior to participation. **Inclusion Criteria:** None given **Exclusion Criteria:** None given
Emilsson S. et al. (2012) [18] *''Support group participation during the post-operative radiotherapy period increases levels of coping resources among women with breast cancer''* Sweden	To investigate whether involvement in a support group while having post-operative radiotherapy impacts: Patients capacity to deal with stress and their cancer. Patients self-reported degree of anxiety and depression.	**Study type**: Non-RCT **Method:** Control group (n=33) Intervention group (n=34) Intervention = Support group participation (5 weeks) during post-operative radiotherapy Questionnaires used: • HADS • CRI Questionnaires given: • Before /Last week of /6 months after radiation therapy.	**Sample size**: 67 **Study population**: Women with breast cancer, attending the Department of Oncology at Umeå University Hospital for post-operative radiotherapy **Inclusion Criteria:** • Radiotherapy referral • Adult • Speak Swedish **Exclusion Criteria:** • Mental/physical disabilities
Björneklett H.G. (2012) [19] *'' Long-term follow-up of a randomized study of support group intervention in women with primary breast cancer''* Sweden	To investigate: The long-term impact of a support group intervention, in a RCT of women with primary breast cancer participating after cancer treatment.	**Study type:** RCT **Methods:** Participants randomised into intervention and controls. The intervention: 1 week of support group participation + 4-day follow-up after 2 months. Long-term follow up questionnaires: • European Organisation for Research and Treatment of Cancer • Quality of Life Questionnaire (EORTC QLQ-C30) • Breast Cancer Module questionnaire (BR 23) • HADS • Norwegian version of the FQ.	**Sample size:** 382 **Study population:** Women with primary breast cancer getting postoperative radiotherapy diagnosed 04/2002 - 11/2007 in Department of Oncology, Central Hospital, Västerås, Sweden. **Inclusion Criteria:** • Primary breast cancer just diagnosed • Physical/mental capability • Survival >12 months expected **Exclusion Criteria:** Individuals with: • Dementia • Serious visual/ auditory/ physically impairments • Severe mental illness • Active alcohol abuse • Prior attendance in group • Hx. malignant disease
Stevinson C. et al. (2011) [20] *'' Cancer support group participation in the United Kingdom: a national survey''* UK	To investigate: The features of support group members on a national scale Links between group and participant variables and outcomes perceived	**Study type:** Cross-sectional study **Method:** • - Postal survey of support groups in the UK. • Group leaders dispersed questionnaires to members. • Data collected on demographic and medical information, group attendance, perceived outcomes and psychosocial variables.	**Sample size:** 841 **Study population:** Cancer patients attending support groups in the UK **Inclusion Criteria:** None given **Exclusion Criteria:** None given

Author (Date) / Title /Location	Key findings	Strengths and Limitations
Batenburg A. et al. (2014) [13] *''Emotional approach coping and the effects of online peer-led support group participation among patients with breast cancer: a longitudinal study''* The Netherlands	***Effect of frequent use of support group:*** i.If approaching emotions less actively => Positive association with increased emotional well-being. i.If actively approaching emotions =>No change in well-being. ***Effect of infrequent use of support group:*** Coping style outweighed effects of online participation; i.If actively approaching emotions =>Increase in psychological well-being. ii. If approaching emotions less actively =>No change in emotional well-being.	**Strengths:** • Longitudinal study: can establish causal relationships. **Limitations:** • Emotional approach to coping, only measured at T0. • Only man in study removed: Results not generalisable to men (Selection bias). • Dropout rate unreported. • No exclusion criteria.
Osei D.K. et al. (2013) [14] *'' Effects of an Online Support Group For Prostate Cancer Survivors: A Randomized Trial''* USA	***Intervention group*** • Improvement in 3/6 statistically significant variables for QOL. • Scores back to baseline by week 8. ***Control Group*** • At 6 weeks, QOL had dropped for 6 of the QOL variables • Scores returned to baseline by week 8	**Strengths:** • First RCT looking at online support for patients with prostate cancer. **Limitations:** • Recruitment= Cancer registry: validity may be affected (external validity + if statistics not free from subjectivity). • Population isn't diverse (education level/ethnicity) + Low response rate: Hard to generalise results. • Long-term effect of intervention couldn't be determined. (8-week study). • Wasn't asked if control group used other resources: Confounding factor. • Inclusion criteria (Aged 40-85) don't match actual population used (Aged 53-87).
Klemm P. (2012) [17] *''Effects of an online support group format (Moderated vs Peer-Led) on Depressive Symptoms and Extent of participation in women with breast cancer''* USA	• Depressive symptoms did not vary significantly by time or group • Moderated group had increased participation in online support group	**Strengths:** • Randomisation **Limitations:** • No selection criteria defined. • More women with increased levels of depressive symptoms randomised to peer-led group. • 'Lurkers': more numerous in peer-led group. • Longitudinal study: Loss to follow (9 dropouts).
Emilsson S. et al. (2012) [18] *''Support group participation during the post-operative radiotherapy period increases levels of coping resources among women with breast cancer''* Sweden	***CRI questionnaire:*** • Study group participants improved coping resources due to intervention. ***HADS questionnaire:*** • No significant variation between the study and control group.	**Strengths:** • Clear selection criteria defined. • All participants received radiotherapy at same hospital- variability minimised. • Non RCT provides a higher level of evidence for causality than observational studies. **Limitations:** • Significant variation found during initial analysis (study vs. control group). • Findings not generalisable + Randomisation not possible: small sample size.
Björneklett H.G. (2012) [19] *'' Long-term follow-up of a randomized study of support group intervention in women with primary breast cancer''* Sweden	i.Significant impact on the following after intervention: • 3 elements in EORTC-QLQ30 and BR 23 **and** • Fatigue (Norwegian version of the FQ) ii. No significant impact on levels of anxiety and depression (HADS).	**Strengths:** • RCT is second only to a systematic review in the hierarchy of evidence. • Relatively large sample size. • Selection criteria clearly defined. • Population was homogenous (women with primary breast ca.). • Long-term follow-up (average 6.5 years) with good response rate. **Limitations:** • During long-term follow-up drop out was marginally higher in the control group: Long-term comparisons between the 2 groups harder. • Participants included in study without prior screening for possible needs: Some may have needed rehabilitation more than others.
Stevinson C. et al. (2011) [20] *'' Cancer support group participation in the United Kingdom: a national survey''* UK	***Socio-demographic:*** • Overrepresented = white (96.8%) female (68.2%). • More participation from men/ those with lower education/ socioeconomic status than in previous studies. ***Perceived benefit:*** • Positive psychological outcomes perceived in women > men. • Frequent meeting attendance (>75%) positively associated with higher reports of benefits.	**Strengths:** • Large sample size. • Nationwide survey. • No loss to follow-up: Cross-sectional study. **Limitations:** • Cross-sectional study: causal relationships cannot be made. • Non-response bias. • No selection criteria defined.

Table 2: Results Summary

Sherman A.C. et al. (2008) [21] *'' Determinants of Participation in Cancer Support Groups: The Role of Health Beliefs ''* USA	To investigate: Group attendance and its associations for patients with varied malignancies getting treatment at a big academic oncology centre	**Study type:** Cross-sectional study **Methods:** • Recruitment: During routine clinic visits • Survey used: created based on the Health Belief Model and literature.	**Sample size:** 425 **Study population:** Outpatients with varied disease sites getting treatment at Winthrop P. Rockefeller Cancer Institute at University of Arkansas for Medical Sciences **Inclusion Criteria:** None given **Exclusion Criteria:** • Time since diagnosis (>4 months) • Inadequate English literacy. • Serious cognitive impairment.
Ussher J.M. et al. (2008) [15] *''A Qualitative Analysis of Reasons for Leaving, or Not Attending, a Cancer Support Group''* Australia	To investigate: Factors that influencing leaving and non-attendance in cancer support groups	**Study type:** Longitudinal, Cross-sectional and qualitative study. **Methods:** • Drop-Outs: Follow-up (12 months): Questionnaire on experience of support group participation. • 87 Drop-outs completed questionnaires with reasons they left. ***Non-Attendees:*** Recruitment: clinics waiting rooms in hospitals. Participants completed: i.Demographic questionnaire ii.Individual or focus group interview.	**Sample size:** 347 in longitudinal study of Drop-Outs + 26 in Cross-sectional study of Non-Attendees **Study population:** • Drop-outs from 47 cancer support groups over 12 months. • Non-Attendees: Patients from 4 oncologists in 3 Sydney hospitals **Inclusion Criteria:** None given **Exclusion Criteria:** None given
Grande G.E. et al. (2006) [22] *''How do patients who participate in cancer support groups differ from* those who do not'' UK	To investigate: The variations between patients with cancer attending community support groups and a random sample of non-attenders on the Cancer Registry	**Study type:** Cross-Sectional Study **Methods:** • Recruitment of support group attendees: Cambridge Cancer Help Centre, community support group for people with cancer. • Comparison sample recruitment: by East Anglian Cancer Intelligence from Cancer Registry records: 200 non-attendees random selection. • Data collected via Cancer Registry records, self-completed and postal surveys.	**Sample size:** 107 (63 participants + 44 non-participants) **Study population:** Not specified. **Inclusion Criteria:** • ≥ 18 years old • Malignant neoplasm diagnosis 1990 - 2002 • No recorded date of death, and residence inside the catchment area of the CCHC. **Exclusion Criteria:** • CCHC members • Patients with no recorded GP
Michalec B. (2005) [23] *''Exploring the Multidimensional Benefits of Breast Cancer Support Groups''* *USA*	To investigate: Variations in breast cancer survivors' quality of life after attendance in a breast cancer support group. If all participants in breast the cancer support groups are uniformly benefiting	**Study type:** Qualitative, Cross-sectional study **Methods:** Data collection: • Telephone interviews • Individual participant-level survey data was joined with tumour registry data (e.g. age and stage at diagnosis)	**Sample size:** 958 **Study population:** Breast cancer survivors on the Eastern North Carolina Tumour Registry. **Inclusion Criteria:** None given **Exclusion Criteria:** None given

Sherman A.C. et al. (2008) [21] *'' Determinants of Participation in Cancer Support Groups: The Role of Health Beliefs ''* USA	***Sociodemographics:*** • Attendance > for Caucasian patients. • Education > in participants than nonparticipants. • Participation > in those with breast cancer or multiple myeloma. **Benefits to attendance:** • Perceived benefits: positively associated with increased group attendance. **Barriers to attendance:** • Geographical barriers (OR = 2.74; CI = 1.09–6.93) • Awareness of support group existence **Facilitators to attendance:** • Increased stress from illness/ disease severity (OR= 4.07; CI= 1.42–11.60) • Encouragement by family or friends (OR= 5.04; CI= 1.98–12.81)	**Strengths:** • Relatively large sample size. • Proportional sampling based on disease site. • Inclusion of patients at different stages of treatment. **Limitations:** • No inclusion criteria defined. • Cross-sectional study: causal links between health beliefs and group participation cannot be established. • Recall bias not controlled for. • Questionnaire not validated. • Results not generalisable to cancer centres in other regions (In sample-gynaecological cancers: underrepresented, haematological cancers: overrepresented).
Ussher J.M. et al. (2008) [15] *''A Qualitative Analysis of Reasons for Leaving, or Not Attending, a Cancer Support Group''* Australia	***Reason for Drop-outs*** Two main reactions: i.Positive outlook on support group: Reasons to leave including practical issues and "time to move on" ii.Negative outlook on support group: Reasons to leave was dissatisfaction (e.g. problem with group leader / organisation). ***Reasons for Not Attending*** i.Individual factors: Avoiding being labelled a "cancer patient," personality issues, and sufficient support already. ii. Group factors: Lack of awareness about groups, practical issues, association of groups with negativity, didn't find a good group.	**Strengths:** • Relatively large sample size for finding the dropouts. • Inclusion of drop outs as well as non-attendees: similar/different reasons for non-attendance elicited. • Longitudinal study design to look at dropouts. **Limitations:** • No selection criteria defined. • Small sample size for the non-attendees + only recruited from hospital clinics (selection bias).
Grande G.E. et al. (2006) [22] *''How do patients who participate in cancer support groups differ from* those who do not'' UK	**Results:** • Support group members: > proportion of younger, educated, female and > users of formal support than control group. • Multivariate analysis determined that independent predictors of group attendance were: i.Views on support group benefits ii.Supportiveness of significant people in terms of attendance ii.Active coping response v.Lack of support system (from a ''special person'')	**Strengths:** • Relatively large sample size. • Selection criteria clearly defined. **Limitations:** • Cross-sectional study: causality cannot be established. • Attendees judged the benefits of support group attendance based on experience, non-attendees judged based on what they thought benefits would be: difficult comparison. • Low response rate in comparison group (28%).
Michalec B. (2005) [23] *''Exploring the Multidimensional Benefits of Breast Cancer Support Groups''* *USA*	**Results:** • Current/past attendance positively associated with increased quality of life versus non- attenders. Association insignificant after controlling for confounding factors. • Attendees vs non-participants, attendees were: i.Younger i.Better income/education levels i.More likely employed and married	**Strengths:** • Regional data used: Decreases selection bias. • Diverse regional population (race, income, place of residence, and education level). • Looks at cancer survivors who have attended any type of breast cancer support groups versus just focusing on a specific support groups type. • Confounding factors accounted for. Limitations: • No selection criteria defined. • Cross-sectional study: causal relationships cannot be derived.

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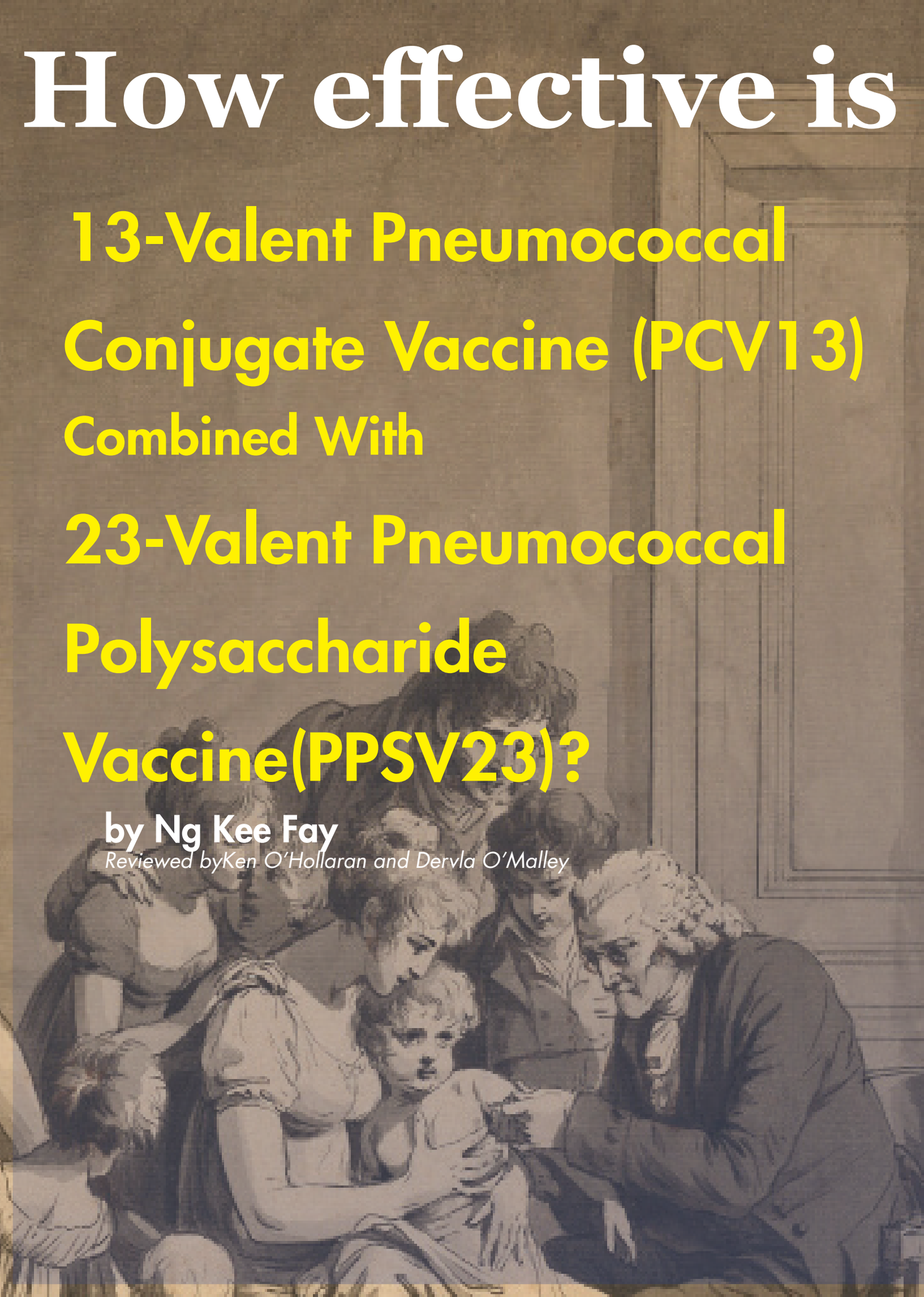
How effective is 13-Valent Pneumococcal Conjugate Vaccine (PCV13) Combined With 23-Valent Pneumococcal Polysaccharide Vaccine(PPSV23)?

by Ng Kee Fay
Reviewed byKen O'Hollaran and Dervla O'Malley



Abstract

The bacterium Streptococcus pneumoniae remains a major cause of morbidity and mortality worldwide. Currently, the 2 leading vaccines targeted against it are: 23-valent pneumococcal polysaccharide vaccine (PPSV23) and 13-valent pneumococcal conjugate vaccine (PCV13). It was only very recently, starting 22 November 2019, that the Advisory Committee on Immunisation Practices (ACIP) no longer recommends routine administration of PCV13 for all adults aged 65 and above. As such, this systematic review aims toinvestigate how the use of PCV13 combined with PPSV23 compares to using PPSV23 alone in older adults.

Relevant research papers were chosen through an electronic search in PubMed. A set of selection criteria was then applied to ensure that the papers aligned with the objectives of this paper.

The majority of the studies included in this paper demonstrated that in adults aged 50 years and above, PCV13 had the ability to generate a strong immune response in adults, even more so than PPSV23 for all of the twelve serotypes common to both vaccines. The safety of PCV13 was also demonstrated in thestudies as no PCV13-related serious adverse events (SAEs) had surfaced. Only one study included in this systematic review opposed the trend.

While the evidence for both PCV13's and PPSV23's ability to generate an immune response have been persuasive, more research that focuses on the clinical endpoint in older adults, as well as the incidence of pneumococcal infections in the population, could be done to fully address the main question of this paper.

Introduction

Pneumococcal vaccinations: An overview

With the bacterium Streptococcus pneumoniae being the most identified pathogen in communityacquired pneumonia, meningitis, as well as human immunodeficiency virus (HIV-1) seropositive individuals [1], pneumococcal vaccination is undoubtedly an important preventive health care measure worldwide. Currently, there exist two vaccines widely available for clinical use: 23-valent pneumococcal polysaccharide vaccine (PPSV23) and 13-valent pneumococcal conjugate vaccine (PCV13). Streptococcus pneumoniae is contained within a polysaccharide capsule and has over 90 distinct capsular serotypes. PPSV23 contains antigens from 23 common serotypes while PCV13 contains antigens from 13 serotypes [2]. There is substantial overlap in theantigens contained within both
vaccines, with 12 of the 13 serotypes found in PCV13 being common to those within PPSV23 (Table1).

A major difference between both vaccines lies in their mechanisms of action. As PPSV23 contains

Table 1: Capsular serotypes found in both PCV13 and PPSV23

Vaccine	Serotypes included
PCV13	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, 23F
PPSV23	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F

purified polysaccharide capsules, it elicits a T-cell independent immune antibody response whichn enhances the activity of phagocytic cells, thereby inducing the killing of Streptococcus pneumoniae. On the other hand, PCV13, being a conjugate vaccine, which combines polysaccharide capsules with carrier proteins, produces a T-cell dependent immune response and hence, a greater potential for immunological memory [3].

In general, routine administration of PCV13 is recommended for all children younger than 2 years of age while routine administration of PPSV23 is recommended for all adults aged 65 and above. 7 The latter is also recommended for people over 2 years of age with certain medical conditions defined as 'at-risk', as per the guidelines of both the Centers for Disease Control and Prevention (CDC) [4]
and the Health Service Executive (HSE) [5].

Use of PCV13 with PPSV23 for older adults

However, the routine uses of PCV13, in combination with PPSV23, for older adults is much less straightforward and has been subject to numerous discussions. In fact, it was only very recently, starting 22 November 2019, that the Advisory Committee on Immunization Practices (ACIP) no longe recommends routine administration of PCV13 for all adults aged 65 and above [6]. Instead, cliniciansare to engage in a discussion regarding PCV13 use with adult patients aged 65 and above who do not have an immune-compromising condition, cerebrospinal fluid (CSF) leak or cochlear implant. Considerations mayinclude the individual patient's risk of exposure to PCV13 serotypes as well as his or her underlying medical conditions [4].

Efficacy of PCV13 for older adults

To complicate matters further, the effectiveness of PCV13 in preventing pneumococcal disease for older adults and above has been challenged. An article has stated that the use ofPCV13 is on a 'much less well-established scientific basis' [7] and another asserted that PCV13 efficacy is not statistically significant [8]. Evidently, there exist many grey areas in the use of PCV13 to be explored.

Objectives

This paper aims to collate and synthesise literature which investigated:

1. The effects of administering both PCV13 and PPSV23 in comparison to administering PPSV23 alone on older adults
2. The safety and efficacy of PCV13 for older adults

Methods

Overview

Appropriate search terms were chosen (Refer to section 3.2) before a list of inclusion/exclusion criteria was defined (Refer to section 3.3). Subsequently, a systematic search strategy was carried out in PubMed. An overview of the methods used

in selecting studies for this paper is illustrated (Figure 1).

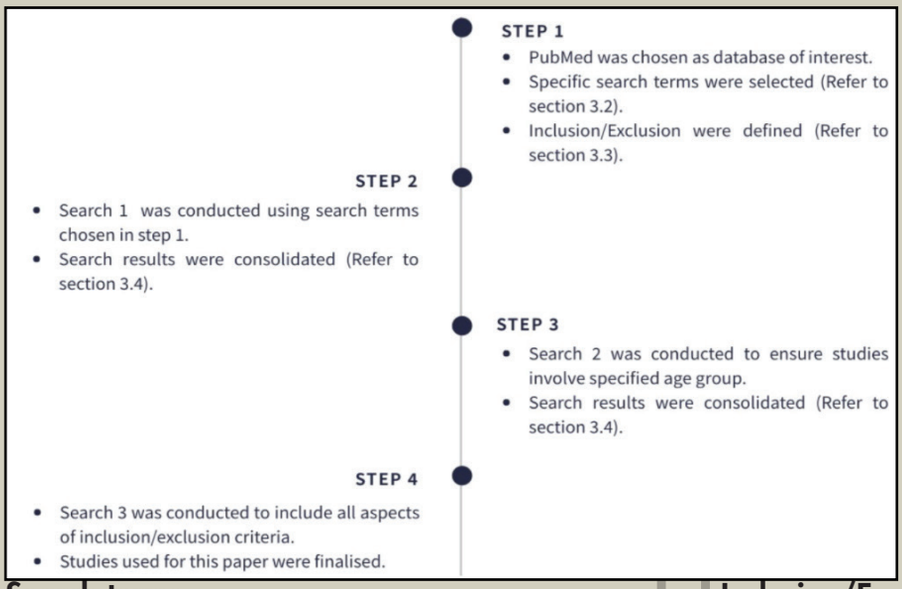


Figure 1:
Overview of methods

Search terms

The following Medical Search Headings (MeSH) search terms were utilised in PubMed:

1. (("23-valent pneumococcal capsular polysaccharide vaccine" [MeSH])
2. "13-valent pneumococcal vaccine" [MeSH])

A Boolean search using 'AND' and 'OR' was conducted.

Inclusion/Exclusion criteria

Subsequently, a set of inclusion/exclusion criteria was designed to further refine and streamline the search process (Table 2).

Details of search strategy

A 3-step approach was taken in selecting the studies from PubMed. The details of each step are described below (Table 3).

Results

Overall evaluation of studies

The final 10 studies selected were then subject to critical appraisal using the Critical Appraisal Skills Programme (CASP) framework. Evaluations of each study are found in Table 4 in the appendix.

Table 2:
Inclusion and exclusion criteria

	Inclusion	Exclusion
Date	Articles published from January 2013 to present	Articles published prior to January 2013
Language	English	Languages other than English
Population of interest	Adults aged 50 and above	Studies that did not include participants aged 50 and above Animal studies
Intervention of interest	Administration of PCV13 Administration of PPSV23	Studies which involved administration of other types of vaccines (e.g., flu vaccine)
Study type	Randomised controlled trials (RCTs) Cohort studies	Cross-sectional studies Case-control studies Opinion pieces Meta-analyses Systematic reviews
Publication	Free full text and abstract availability	Free full text and abstract unavailable
Outcome of interest	Efficacy of vaccines on older adults	Any other outcomes irrelevant to study

	Search terms/Scope of search	Objective of search	Results from PubMed
Search 1	Refer to section 3.2	To gather all relevant studies	56
Search 2	Search 1 AND population of interest	To ensure that the studies selected only involve population of interest	17
Search 3	Search 1 AND 2 with application of inclusion/ exclusion criteria	To ensure that all the studies chosen are fully relevant to the objectives of this paper	10

Table 3: Details of search strategy

Comparison between PCV13 and PPSV23

Schmoele-Thoma et al. found that in the PPSV23/ PCV13 group (PPSV23-pre immunized adults who received subsequent PCV13), the opsonophagocytic activity (OPA) geometric mean fold-rise (GMFR) was >1 for most serotypes. Additionally, OPA geometric mean titers (GMTs) were numerically higher for 12 out of 13 serotypes after a second PCV13 vaccination than after the first dose of PCV13. In addition, among the PPSV23-naive subjects, the highest GMFRs were found in the PCV13/PPSV23 group (along with the PCV13/PCV13 group) for all serotypes other than serotype 5 [9].

In the Jackson et al. study, OPA GMT ratios comparing the PCV13/PPSV23 and PPSV23 groups were >1 for all 13 serotypes [10].

In the study conducted by Jackson et al., for the 60-64 years age group, PCV13 OPA GMTs were noninferior to PPSV23 for all 12 common serotypes and statistically significantly greater in 8 11 serotypes. Additionally, OPA GMTs in 50–59-year-olds were noninferior to 60–64-year-olds for all 13 serotypes, and were statistically significantly greater in 9 serotypes [12].

Shiramoto et al.'s study found that GMFRs post-vaccination were higher for PCV13 recipients than in PPSV23 recipients for all serotypes except serotype 3 [16].

Efficacy of PCV13

In the Schmoele-Thoma study, among PPSV23-naive subjects, the highest GMFRs were found in the PCV13/PCV13 group alongside the PCV13/PPSV23 group for all serotypes except serotype 5 [9].

The Jackson et al. study indicated that OPA GMTs following administration of a 2nd dose of PCV13 (PCV13/PCV13) were statistically significantly greater than 1 dose of PCV13. However, 3 serotypes yielded inferior responsesin the 50-59-years age group (GMT ratios <1). Additionally,the Jackson et al. study noted that OPA GMTs following a second dose of PCV13 (PCV13/PCV13)were numerically greater than following a second dose of PPSV23 (PPSV23/PPSV23) [10].

The Vila-Corcoles et al. study stated that unadjusted incidence rates (per 100,000 person-years) for pneumococcal pneumonia were higher in PCV13-vaccinated than unvaccinated populations(289.3 and 82.1, respectively). The trend persists in all-cause pneumonia and all-cause death. Even following multivariable adjustments, PCV13 was not found to be effective [11].

Solanki et al. found that the GMFRs before and approximately 1 month after PCV13 administration in the participants ranged from 6.6 to 102.7. No statistically significant differences in immune responses were observed between the 50-59-years and 60-64-years age groups [13].

OPA GMFRs in the Tinoco et al. study showed a significant increase in OPA GMTs from immediately before to 1 month after PCV13 vaccination. OPA GMFRs were higher in the 50-64-year age

group (ranges from 5.3 to 63.6) than the ≥65-year age group (ranges from 3.4 to 35.8) [14].
12 In the CAPiTA trial conducted by van Deursen et al., OPA GMTs in PCV13 recipients increased at 1-month post vaccination and decreased at 12- and 24-months post-vaccination but remained above baseline for all serotypes (GMFRs remained >1). The IgG geometric mean antibody concentrations (GMCs) showed a similar trend. In addition, OPA GMFRs and IgG GMCs in PCV13 recipients aged ≥80 years were generally lower than in younger recipients [15]. In Bonten et al.'s per-protocol analysis, vaccine efficacy for community-acquired pneumonia (CAP), non-bacteremic and non-invasive CAP as well as invasive pneumococcal disease (IPD) were 45.6%, 45.0% and 75.0%, respectively. Similar efficacy for all3 end points was observed in the modified intention-to-treat analysis (37.7%, 41.1% and 75.8%), but not for CAP from any cause (vaccine efficacy: 5.1%) [18].

Safety of PCV13

After multivariable adjustments, Vila-Corcoles et al. stated that PCV13 was found to not cause significant alterations in the risks of pneumococcal pneumonia (multivariable Hazard Ratio [mHR]: 1.17) or all-cause death (mHR: 1.07), though its association with increased risk of all-cause pneumonia remained significant (mHR: 1.69) [11]. In the studies conducted by Jackson et al. [12], Solanki et al. [13], Tinoco et al. [14], Bonten et al. [18] and Shiramoto et al. [16], no vaccine related SAEs or deaths were reported.

Efficacy of PPSV23

Jackson et al. discovered that OPA GMTs following revaccination of PPSV23 were statistically significantly lower for 9 serotypes when compared to those following initial administration of PPSV23, with a GMT ratio of less than <1 for all 9 serotypes. OPA GMTs were non-inferior for 4 serotypes [10]. The study conducted by Shiramoto et al. showed that OPA GMTs 1-month post-vaccination increased significantly in PPSV23 recipients, with GMFRs ranging from 8.2 to 65.4 for all 12 serotypes found in common with PCV13 [16].
13 Following multivariable adjustments by Ochoa-Gondar et al., they reported that recent vaccination with PPSV23 (<5 years ago) was associated with decreased risk of bacteremic pneumococcal CAP(HR:0.38), non-bacteremic pneumococcal CAP (HR: 0.52) and all-cause CAP (HR: 0.75) [17].

Discussion

Overall choice of studies

Of the 10 studies, 8 are RCTs while 2 are prospective cohort studies. The former is regarded as themost reliable form ofscientific evidence in the hierarchy of evidence [19]. The latter is considered to provide stronger evidence than other observational studies as exposure is identified before outcome [20]. Sample sizes were generally large, ranging from 322 to 2,025,732, which aided in providing more credible results with greater precision. It is worth noting that Tinoco et al. [14], whose study had the smallest sample size, utilised statistical methods to ensure that the sample size was sufficient in providing adequate precision in the results.

Use of both PCV13 and PPSV23 vaccines in older adults

There is consensus among the studies that PCV13 was able to elicit robust immune responses in-adults aged 50 years and above. While most of the studies utilised OPA GMTs as evidence, Bontenet al.'s [18] use of the incidences of diseases was able to prove the same point. Although theefficacy of PPSV23 has also been demonstrated in the studies conducted by Jackson et al. [10],Shiramoto et al. [16] and Ochoa-Gondar et al. [17], all studies that compared immune responsesbetween PCV13 and PPSV23 have shown that PCV13 was able to produce greater immuneresponses for all 12 serotypes common to both vaccines (Refer to section 4.2). However, there are slight disagreements among studies which compared post vaccination immune responses between different age groups. While the Jackson et al [12] and van Deursen et al. [15] studies found that older age groups (60-64 years age group and ≥ 80 years age group, respectively)have decreased immune responses following PCV13 vaccination, the Tinoco et al. [14] and Solanki et al. [13] studies found no significant differences between the immune responses across age
14 groups. Interestingly, all four studies share a common limitation of being done in a single country, which could possibly explain the differences in their findings. Nevertheless, immune

responses remained greater than pre-vaccination levels across all studies, which once again proved PCV13's ability to generate an immune response in adults aged 50 and above. Four studies also found that PCV13 was generally safe and well-tolerated in adults aged 50 years and above, as no PCV13-related SAEs or deaths were reported.
The only study that refutes the consensus, both in terms of the efficacy and safety profile of PCV13, is the cohort study conducted by Vila-Corcoles et al. [11]. Its major limitations lie in its nonrandomised, observational nature and that it was made in a single geographical region, Catalonia. Logically, PCV13 efficacy varies across different geographical settings and depends on multiple factors such as PPSV23 coverage as well as susceptibility for pneumococcal infections among the population. However, it is noteworthy that the authorsacknowledged the inherent limitations of this study and adjusted accordingly, such as performingmultivariable analysis, and the study provided valuable data from a clinical and public health point of view.
Considering all of the evidence, this review concludes that the use of PCV13 with PPSV23 would be able to provide a greater immune response (measured by OPA GMTs and GMFRs as well as IgG GMCs) when compared to receiving PPSV23 alone for older patients aged 50 and above.However, to answer the question of whether the former is truly superior to the latter, more studies would need to be reviewed.

Limitations

A limitation of this literature review arises from the limited number of studies chosen for this review. Most studies focused on the immune response in terms of OPA GMTs following the use of PPSV23 and PCV13 rather than the efficacy of both vaccines on clinical endpoints.
Additionally, it would have been useful to study the impact of introducing PCV13 to the paediatric population on the incidence of pneumococcal strains in the population. Examining these topics [15] could possibly help navigate questions surrounding the necessity of PCV13 in older populations, hence allowing the main clinical question of this paper to be better understood with greater breadth and depth.

Future research

While reviewing the selected studies, other exploratory areas such as the impact of age on the immune responses elicited in vaccinated patients as well as the duration of protection conferred byboth vaccines emerged. Hence, RCTs focusing on these specific areas are highly desirable. In addition, more data regarding the sequential use of both vaccines would be beneficial.

Conclusion

In conclusion, evidence hasshown that each vaccine can generate immune responses on their own. While PPSV23 covers a greater number of serotypes, PCV13 seems to produce a greater immuneresponse for the 12 serotypes common to both vaccines. The combination of both PPSV23 and PCV13 should provide a greater immune response than just receiving PPSV23 alone in adults aged 50 and above. However, as for determining whether the use of PCV13 alongside PPSV23 is indeed necessary and superior to just using PPSV23, there is still room for research asthe choice is a multifaceted one in which other aspects such as the impact of both vaccines on age as well as various clinical endpoints should be considered.[16]

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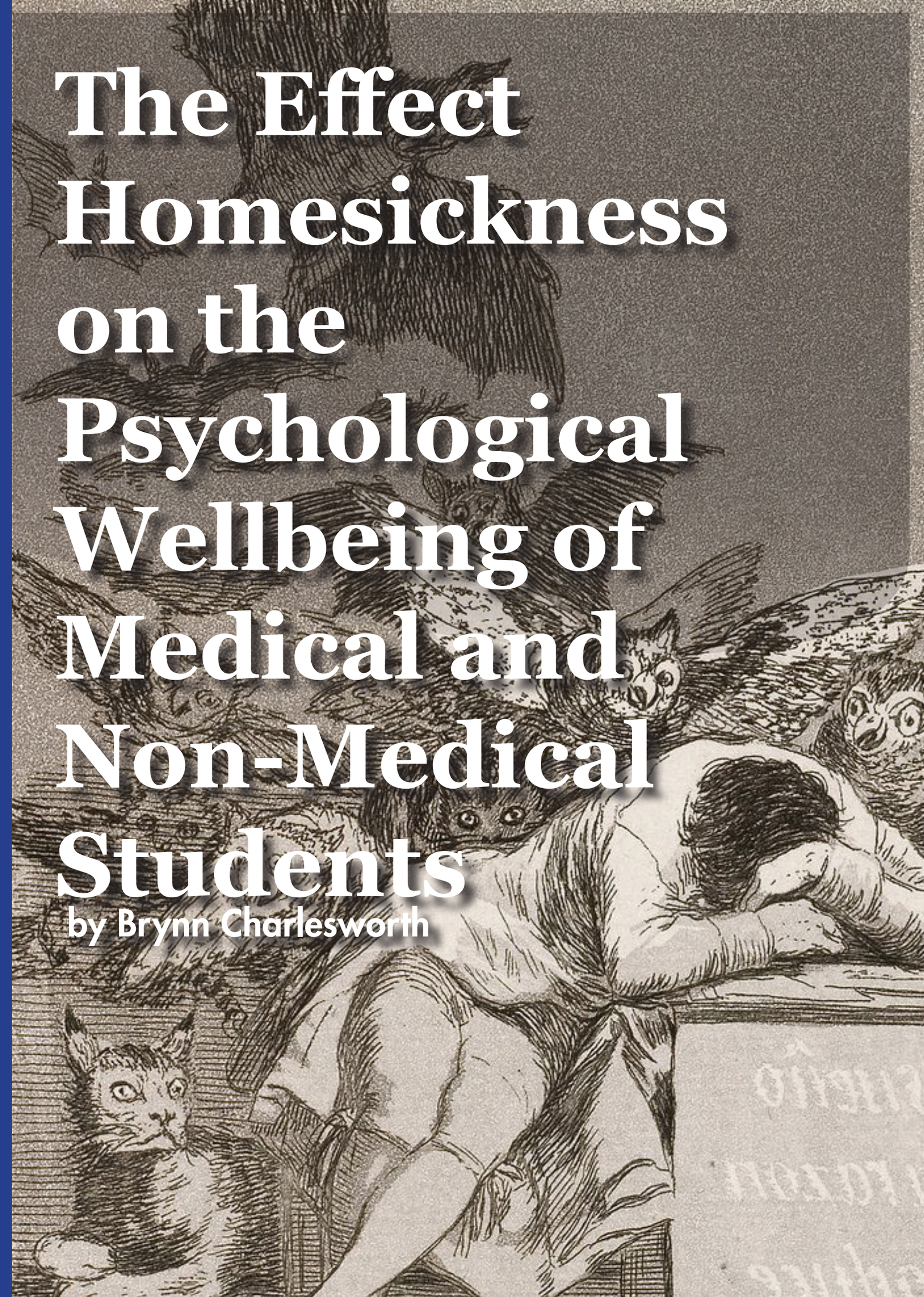

The Effect Homesickness on the Psychological Wellbeing of Medical and Non-Medical Students

by Brynn Charlesworth

Abstract

Introduction

Homesickness commonly affects students moving to college for the first time, causing physical, psychological, and emotional disturbances. Medical students are particularly vulnerable to distressing feelings due to the already high prevalence of mental illness and burnout within this population.

Aims & Objectives

This review aims to critically evaluate the current literature on homesickness and wellbeing of postsecondary students, assessing the impact of psychological distress and investigating the relationships between mental illness, medical student burnout, and their implications in medical school.

Methods

Searches of PubMed, PsychINFO, and Psychology and Behavioural Sciences Collection databases were conducted to analyse literature on homesickness, student wellbeing, and burnout. These were screened according to pre-defined criteria and articles were assessed for appropriateness.

Results

12 articles successfully met the eligibility criteria. Homesickness was found to affect the majority of freshman students, associated with both a significant decrease in college adjustment and an increase in depression. Within the postsecondary population, psychological distress varied, with medical students having poorer mental health than their peers. The risk for burnout was found to be predictive of mental illness and was associated with unprofessional behaviour.

Discussion

During the transition to college, students are under an enormous amount of pressure – academically and psychologically. Evidence suggests that homesickness is common, with associations found between homesickness and depression. A high prevalence of psychological distress among the postsecondary population and a positive correlation between mental illness and burnout was also found. As such, medical student homesickness and burnout should be investigated to decrease potentially devastating consequences.

Reviewed by John Mackrill and Mohammad Abdulla

Introduction

Homesickness is defined as "the distress or impairment caused by an actual or anticipated separation from home" and is considered a subconstruct of acculturative stress (1, 2). With higher education being marked by considerable change and transition, students moving for the first time are vulnerable to this feeling of distress (3). Those who have experienced intense homesickness have described symptoms including unstable emotions, isolating thoughts, severe loneliness, inability to concentrate, fluctuating sleep patterns, diet disturbances, and nausea, mirroring symptoms experienced in mental ill-health and grief (2, 4, 5). Previous research found homesick women reported decreased physical wellbeing, intellectual function, and overall mood (6). While this feeling of distress can affect anyone, homesickness is commonly experienced by individuals away to university (2, 7). People are distanced from their previous support network with simultaneous exposure to new stressors and challenging environments (2, 7). With over 5.3 million students studying outside their home country and projections showing continuous global growth, understanding the effect of homesickness in higher-level education is imperative (8, 9).

While much of the past research has focused on the personal risks and preventative factors of homesickness of first-year students, this review intends to consolidate the current literature on homesickness and mental health status in tertiary education (10-12). It will amalgamate data on the impact of mental illness within the postsecondary population, with an emphasis on a high-risk sample of medical students. Studies have suggested that a consistently higher prevalence of psychological distress exists among medical students compared to the general population and their non-medical peers (13). Further, burnout among medical school graduates has been recognized as a public health emergency, with over 80% of doctors at significant risk (13). With the emerging mental health crisis among medical students, the effect of psychological distress on medical student burnout will also be examined (14).

By elucidating the relationship between homesickness and wellbeing in students, this review will provide a foundation for third-level institutions to facilitate transition into postsecondary education, assist homesick students, promoting an environment allowing students to flourish. Further, by exploring the negative outcomes associated with mental ill-health in the medical student population, efforts can be made to decrease potentially devastating consequences to individual wellbeing, patient care, and the overall healthcare system.

Abbreviation	Meaning
AEQ	Achievement Emotions Questionnaire
ASSIS	Acculturative Stress Scale for International Students
AVEM	Work-Related Behavior & Experience Pattern
CES-10	Center for Epidemiologic Studies Short Depression Scale
GHQ12	General Health Questionnaire
HADS-D	Anxiety & Depression Scale
MBI	Maslach Burnout Inventory
MBI-GS	Maslach Burnout Inventory - General Survey
MBI-SS	Maslach Burnout Inventory - General Survey for Students
PHQ-9	Patient Health Questionnaire
PMSS	Perceived Medical School Stress
PRIME-MD	Primary Care Evaluation of Mental Disorders
SES	Socioeconomic status
SF-8 QOL	Medical Outcomes Study Short-Form Quality of Life
UHS	Utrecht Homesickness Scale
UNE	University of New England

Table 1: Abbreviation used

Reason for Exclusion	Number
Review objectives not directly addressed (narrow scope)	10
Intervention implementation as primary focus (incorrect topic)	7
Systematic review (incorrect source)	5
Study population limited (highly specific)	3
Qualitative analysis (incorrect source)	2
Full free text unavailable (not accessible)	1
TOTAL	28

Table 3:
Rationale for literature exclusion

Aims & Objectives

This review aims to summarize, analyse, and evaluate the current literature on homesickness and wellbeing of postsecondary students, and the corresponding effect on burnout, by:

1. Examining the effect of homesickness on the wellbeing of postsecondary students;
2. Assessing the impact of mental ill-health in the postsecondary and medical student population;
3. Exploring the relationship between mental illness and medical student burnout;
4. Investigating the consequences of burnout in medical school.

Methods

Search Strategies

To identify the literature which satisfy the objectives of this review, four electronic searches were conducted on the 9th January 2020. Three databases were used. Final search terms were as follows:

PubMed & PsychINFO
(higher education OR tertiary education OR third-level education OR postsecondary* OR university students OR college students) AND (homesick* OR student homesick*) AND ((student mental health OR mental health OR mental well-being OR mental wellbeing OR psychological stress OR mental pressure) OR (prevalence OR statistic*))

PsychINFO & Psychology and Behavioural Sciences Collection
(student burnout OR medical student burnout OR medical student distress) AND (risk factors OR contributing factors OR predisposing factors OR predictor OR cause OR correlation) AND (medical school OR medical student OR medical undergraduates

Selection Process

After the initial searches were conducted, a total of 140 results were found on the databases. An additional 4 papers were discovered from the references of the aforementioned results. A total of 12 successfully met the entire eligibility criteria and were read in full to be included for review.

Inclusion Criteria	Exclusion Criteria
Equivalent subjects	Highly specific & limited study population
Peer reviewed	Systematic reviews
Quantitative research	Qualitative research
Full text	Full free text unavailable
Publication year: 2009-2019	Only one component of objective addressed
Population group: humans	Research on mental health interventions
Language: English	

Table 2:
Criteria to determine study eligibility

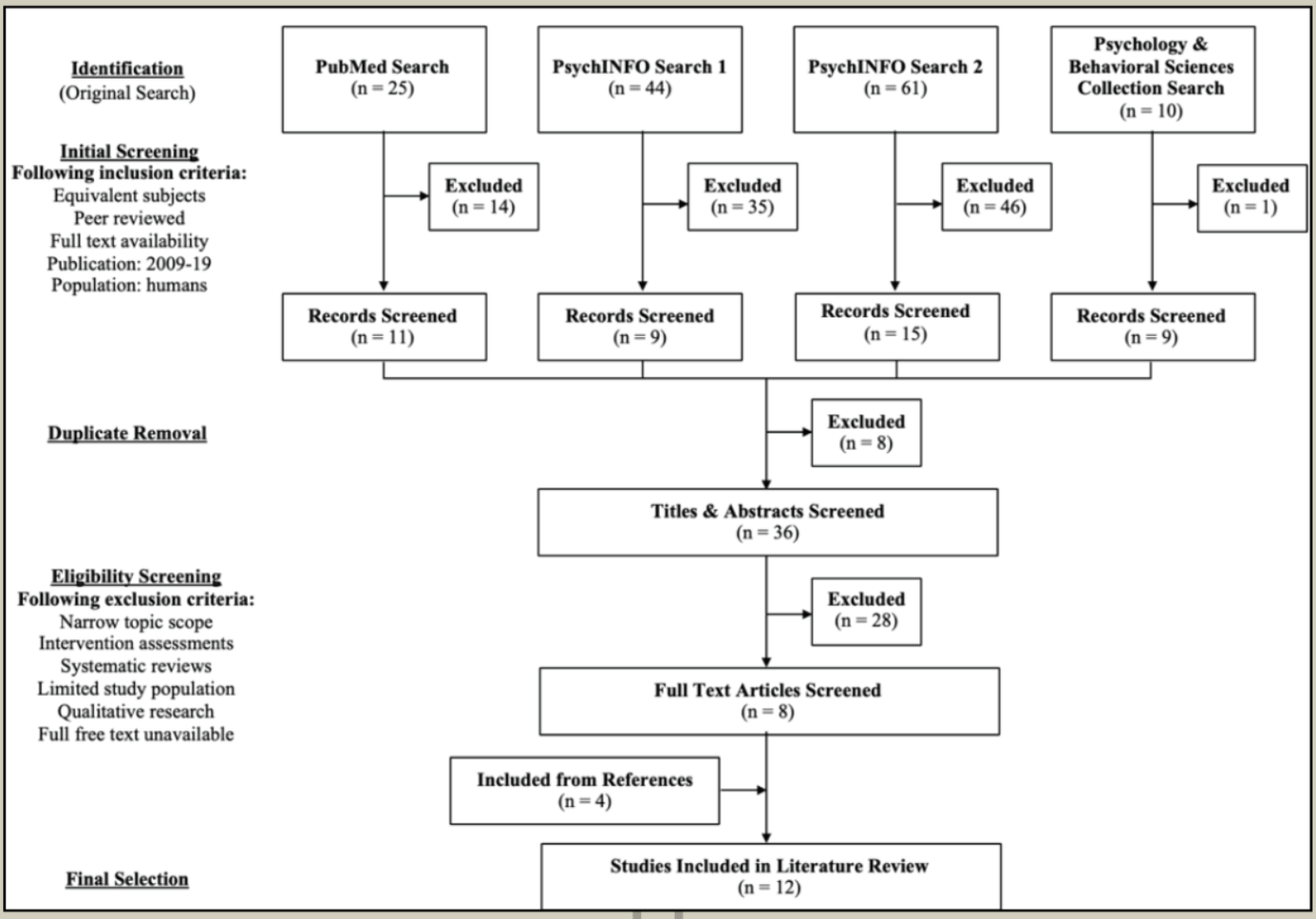

Figure 1:
Literature Search Strategy: Identification to selection

Data Collection

Information was obtained and critically assessed using the EBL Checklist and all 12 articles were determined to be high quality.

Results

Following the appraisal, data was collected from 10 cross-sectional and 2 longitudinal studies. Analysis of the studies has provided a deeper understanding of homesickness, wellbeing, and burnout in the postsecondary population.

Homesickness & Student Wellbeing

A study of undergraduates who had moved away from home found that 94% experienced homesickness within the first 10 weeks of their freshman year, where level of homesickness was found to decrease throughout their first semester (15). Homesickness was found to lead to a significant decrease in college adjustment, negatively correlated with social and academic life satisfaction, feeling settled at school, and relationship quality at college (15). Females were found to have a higher prevalence of homesickness & a significant positive predictors of homesickness included feeling the need to belong (16). Alternatively, a significant negative predictor was the feeling of acceptance in the new location, independent of the number of friends made (16). Furthermore, homesickness was found to be positively correlated with depression, acting directly and indirectly through self-confidence (17).

Psychological Wellbeing in the Postsecondary & Medical Student Population

Significant differences in mental illness were found to exist across different demographics, including place of origin, relationship status, and gender (17, 18). One study found that depression scores were highest among international students from Africa and Asia relative to their peers elsewhere (17). Married students were also found to have significantly higher levels of depression

Reference	Population Validity	Data Collection Validity	Study Design Validity	Results Validity	Overall Validity
1	83.3%	71.4%	100.0%	83.3%	84.6%
15	100.0%	85.7%	80.0%	100.0%	91.7%
16	87.5%	100.0%	80.0%	100.0%	92.0%
17	83.3%	71.4%	100.0%	83.3%	84.6%
18	100.0%	100.0%	100.0%	83.3%	95.6%
19	83.3%	71.4%	100.0%	83.3%	83.3%
20	100.0%	83.3%	100.0%	83.3%	91.3%
21	83.3%	83.3%	100.0%	100.0%	91.3%
22	83.3%	87.5%	100.0%	83.3%	87.5%
23	100.0%	83.3%	100.0%	83.3%	91.3%
24	100.0%	100.0%	100.0%	100.0%	100%
25	83.3%	57.1%	80%	83.3%	75.0%

Table 4:
Study Validity

compared to those who were single (17). However, it should be noted that the study did not include if this data pertained only to long-distance relationships (17). While one study did not find a significant difference between gender in the general postsecondary population, others found that female medical students were more likely to have moderate-severe depression (17-19). Male medical students were more likely to have depression rather than anxiety (17-19). Additionally, significant positive correlations of depression with homesickness, poor cultural competence, and low self-confidence were found to exist (17).
Further investigation into the medical student population revealed that 62% and 92% of medical students were classified as having minor psychiatric illnesses in India and Jordan, respectively (20, 21). Specifically, 2-10% of students were previously diagnosed with a mental illness before entering medical school and an additional 5-11% were diagnosed while in the program (20, 21). One study found that 14.3% of their students had moderate-severe depression and 22% had been suicidal since beginning the program, with students in their clinical years more likely to report suicidal ideation (18). Another study found that medical students had poorer mental health than age-matched references, with significant differences in mean scores between these two groups (19).

Psychological Wellbeing and Medical Student Burnout

Using the MBI, 26.4-52.8% of medical students presented with burnout, increasing to 71% when examining the preclinical years alone (22-24). In particular, subscales of the MBI determined 70.6% had high emotional exhaustion, 52.8% high cynicism, and 48.7% low academic efficacy, with personal characteristics accounting for 14.4% of burnout variability (23). A cross-sectional study found first-year students at the highest risk of burnout; however, a longitudinal study found the proportion of students at risk increased throughout their medical education (19, 23).

Consequences of Medical School Burnout

The risk for burnout was found to be predictive of depression and anxiety among medical students, positively correlated with sleep deprivation and unprofessional behaviour (19, 24). Whereas altruistic views of the societal responsibility of physicians, feelings of control, and professional self-confidence were found to be negatively correlated (19, 22, 24). Burnout was the only feature of distress with a direct effect on these views and behaviours (24).

Discussion

Key Findings

The majority of students (94%) were found to experience homesickness at the beginning of college with feelings of distress caused by displacement from the home decreasing their satisfaction with student life, ability to form new relationships, and overall college adjustment (15). With the established link between homesickness and depression and the high prevalence of mental illness among the postsecondary population, especially among medical students, students are under both immense psychological stress and academic pressure (17-21).

Title (Reference)	Design, Setting & Participants	Main Outcome Measures
Acculturative stress and influential factors among international students in China: A structural dynamic perspective (1)	Analysis of a cross-sectional International Student Health & Behaviour Survey among all international students enrolled at 4 universities in Wuhan, China (n = 567)	• *Acculturative stress* – ASSIS
Homesickness and adjustment across the first year of college: A longitudinal study (15)	Weekly, longitudinal surveys among all freshman students who moved away from home & were enrolled at a university in the United States (n = 174)	• *Homesickness* (single item measure) • *Emotional experience* • *Adjustment to college* • *Social network* – a measure of contact frequency, contact, enjoyment, difficulty & emotional support • *Social & academic adjustment* – measure of social & academic adjustment • *Global adjustment* to college – SWLS
Effects of social belonging on homesickness: An application of the belongingness hypothesis (16)	Study 1: Cross-sectional survey administered to all international students enrolled at 5 universities in Australia (n = 161) Study 2: Experimental design conducted in the first 6 school among all new intake students enrolled at the University of New England (UNE) in New South Wales (n = 144)	• *Homesickness* – modified UHS • *Chronic need to belong* – measure of individual differences • *Contact with home* – measure of interaction with family & friends over 4 weeks • *Social network in Australia* – measure of the number of relationships students had in Australia • *Social activity* – measure of the frequency of which the student goes out socially • *Acceptance by Australians* – modified Nesdale & Mak Acceptance Scale
Path analysis of acculturative stress components and their relationship with depression among international students in China (17)	Analysis of a cross-sectional International Student Health & Behaviour Survey among all international students enrolled at 4 universities in Wuhan, China (n = 567)	• *Acculturative stress* – ASSIS • *Depression* – CES-10
Depression, stigma, and suicidal ideation in medical students (18)	Cross-sectional survey among students enrolled at the University of Michigan Medical School in the United States (n= 769)	• *Depression* – PHQ-9 • *Stigmatizing views* – measures attitudes about mental illness &mental health care seeking • *Key influencing factors* – measure of diagnosis/treatment of depression & stress/coping in medical school
Perceived medical school stress and the development of behavior and experience patterns in German medical students (19)	Weekly, longitudinal surveys administered to first, second- & fifth-year medical students at Lübeck Medical School in Northern Germany (n = 182)	• *Professional Distress* – AVEM • *Stress perception* – a modified PMSS questionnaire • *Subjective health* – Short Form-12 Health Survey measure of 8 dimensions of health • *Psychological disturbances* – HADS-D
Wellbeing and burnout in medical students in India; A large-scale survey (20)	Cross-sectional survey among students enrolled at 4 major medical schools in India (n = 597)	• *Burnout* – Oldenburg burnout ratings • *Substance abuse* – CAGE questionnaire • *Minor psychiatric disorders* – GHQ12
Wellbeing and mental health amongst medical students in Jordan: A descriptive study (21)	Cross-sectional survey among students enrolled at 5 medical schools in Jordan (n = 479)	• *Burnout* – Oldenburg burnout ratings • *Substance abuse* – CAGE questionnaire • *Minor psychiatric disorders* – GHQ12
The prevalence and correlations of medical student burnout in the pre-clinical years: A cross-sectional study (22)	Cross-sectional among students enrolled at Mount Sinai School of Medicine in New York (n = 86)	• *Professional distress* – MBI-GS measure of emotional exhaustion, depersonalization & personal accomplishment • *Sleep deprivation* – Epworth Sleepiness Scale
Burnout among medical students during the first years of undergraduate school: Prevalence and associated factors (23)	Cross-sectional survey among all undergraduate medical students enrolled at Barretos School of Health Sciences, Dr. Paulo Prata in São Paulo, Brazil (n = 330)	• *Professional distress* – MBI-GS for Students measure of emotional exhaustion, cynicism & academic efficacy • *Daily regimes* – measures of academic, personal & outside-of-school domains
Relationship between burnout and professional conduct and attitudes among US medical students (24)	Cross-sectional survey among students enrolled at 7 medical schools across the United States (n = 4400)	• *Professional distress* – MBI measure of emotional exhaustion, depersonalization & personal accomplishment • *Depression* – PRIME-MD depression screening instrument • *Personal distress* –SF-8 QOL assessment tool • *Professionalism* – measure of professional attitudes & conduct
The relationship of emotions and burnout to medical students' academic performance (25)	A total of 4 cross-sectional survey among first- & second-year undergraduate medical students in the Midwest of the United States (n = 264)	• *Professional distress* – MBI-SS measure of emotional exhaustion, cynicism & academic efficacy • *Achievement emotions* – a modified AEQ measure of hope, pride, shame & anxiety subscales • *Academic performance* – final overall percentage for the semester

Table 5:
Summary of Studies

This review identified a relationship between mental illness and medical student burnout, which was pervasive across all years of study (19-21, 23). School stress and burnout predicted poor mental health and performance and up to 22% of medical students considered killing themselves whilst in the program (18, 19). Burnout was found to be associated with physical, emotional, and professional deficits as well, underscoring the negative impact of burnout in the healthcare field (22, 24, 25). These findings build upon the extensive body of evidence that indicates the relationship between higher levels of burnout in the clinical

environment and lower-quality patient care and satisfaction, increased medical errors, decreased professionalism, and reduced efficacy (26). Mental health problems have devastating consequences that medical professionals will continuously face throughout their careers. Evidence suggests that preclinical medical students appear to be affected by a complicated web of burnout, mental illness, and homesickness, predisposing students to an enormous amount of stress. This compromises their feelings of professional self-confidence immediately before entering the clinical field. As such, students in the early years of medical education must be provided with the necessary resources to help develop coping mechanisms needed to limit detrimental effects.

Study Quality, Strengths & Limitations

All studies were critically appraised and deemed high quality using the EBL Checklist, with overall validity scores ranging from 75-100%. Values were achieved by consistent population representation, acquisition of informed consent, use of transparent methodology, and suggestions for future research.

With self-reporting of sensitive topics, these questionnaires were vulnerable to recall, volunteer, and social desirability biases. Further, the scales measuring mental wellbeing may have been skewed based on the participant's mood or stress level. Nevertheless, many of the studies had large sample sizes and adequate response rates to minimize errors and increase validity. Confidentiality was also ensured to encourage truthful responses by participants. Additionally, while an array of confounds were adjusted for, it is possible that other factors were not accounted for and potentially altered results, such as the depth of friendships, the overrepresentation of women, and socioeconomic status (1, 16, 18).

Furthermore, 10 studies included in this review were cross-sectional in nature. As such, the majority of the research was correlational and provided associations between homesickness, mental illness, student burnout, and their associated consequences. To provide a more complete picture of the connection between these factors, an additional 2 longitudinal studies were also included to explore their causative relationships. Also, 5 were single-centre studies limiting the generalizability of the results; however, data was collected from students from up to 94 countries, studying across 5 continents.

Lastly, while many of these studies used the same validated instruments, variation did exist. Of the 7 studies investigating medical student burnout, 3 different instruments were used. Therefore, caution should be taken when directly comparing these results, as underlying subconstructs differ slightly.

Future Research

Studies should be conducted to replicate results found, across various populations including different institution types, disciplines, years of study, and ethnic backgrounds to verify findings and allow broader inferences to be made (25). Causative factors should be determined to establish directionality and to identify targets for interventions aimed at decreasing the level of homesickness, psychological stressors, and negative outcomes among students, as homesickness prevention programmes facilitating a healthy adjustment to college are rare (2). Due to the vast population in postsecondary institutions with varied cultural backgrounds, continued research into the effect of interpersonal skills, interactive stressors, and intrapersonal factors on homesickness should be undertaken to develop programmes for students best suited to their needs (1, 16, 17).

Conclusion

Evidence suggests that homesickness is common among all university students and poorer mental health is associated with increased homesickness. With the higher prevalence of mental illness in medical school and the negative impact of psychological stress on individual wellbeing and patient care, further research is needed. Specifically, investigation into the relationship between medical student homesickness and level of burnout and how it affects their overall wellbeing, and the healthcare system is essential.

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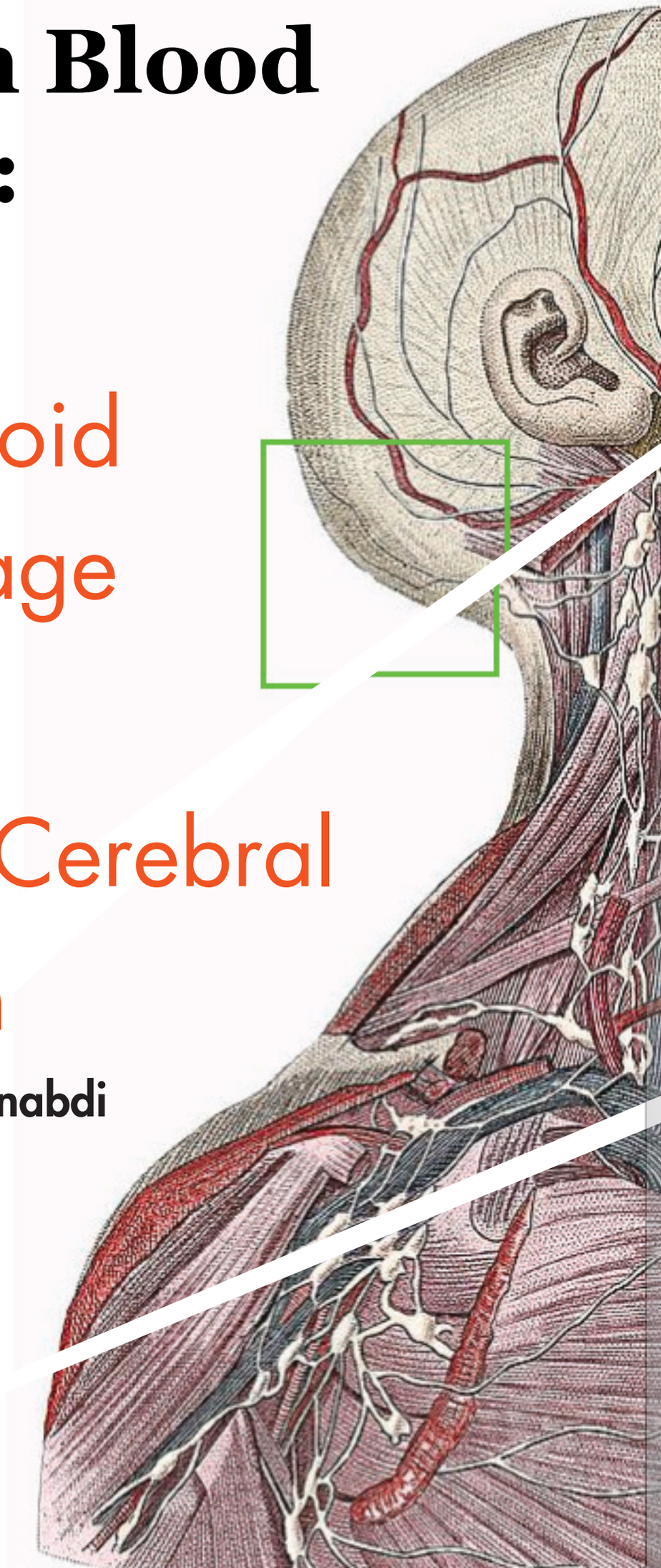
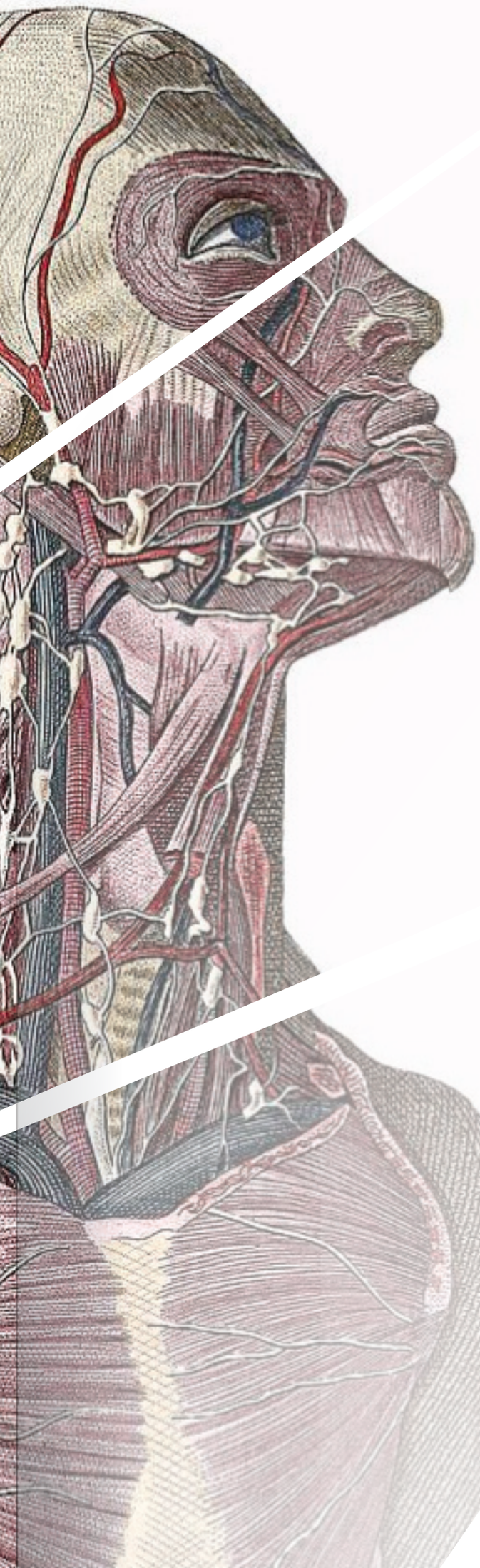
Trends in Blood Pressure:

Following Subarachnoid Haemorrhage and Preceding Cerebral Vasospasm

by Ali Abdulghani Binabdi





Abstract

Background

Trends in Blood Pressure (BP) following Subarachnoid Haemorrhage (SAH) have been reported in literature since 1982 (1). Recent studies suggest a correlation to the incidence of Cerebral Vasospasm (2, 3). This renders BP a candidate for possible early detection of Vasospasm. However, conflicting results regarding the nature and numerical of this correlation exist.

Objectives

To determine trends in BP following SAH in terms of Systolic (SBP), Diastolic (DBP) and Mean Arterial Pressure (MAP) and collaborate current literature evidence of their association to Cerebral Vasospasm.

Methods

Two databases (EBSCO Medline and PubMed) systematically reviewed using specified search criteria. Thirteen studies were portrayed, of which ten were accessible. Thorough critical appraisal of each paper was then manually performed using the CASP Cohort study checklist.

Results

A consistent pattern of change is seen through time in majority of studies with differences in the definite values of the BP variables. Collation of results showed a gradual rise in SBP followed by a plateau of 154.08 (±10.79) mmHg on days 4-8 post-SAH. Variations exist with regards to the association with Cerebral Vasospasm: a third of the studies depicted a significant steeper rise in SBP in Vasospasm patients (1-3), another third conversely reported sudden drops in SBP (4-6), and one study concluded that MAP has no significant relation to Vasospasm (7).

Conclusion

A biphasic trend is expected following SAH with an initial gradual rise followed by a sustained hypertensive plateau. Considerable conflict exists in the nature of association between BP and Vasospasm. Further analysis of such beneficial predictive potential is recommended for advancement in Vasospasm and Neuro-Cardiogenic care.

Introduction

Cerebral Vasospasm is defined as the narrowing of the large and medium intra-cranial arteries. It is a major complication following Subarachnoid Haemorrhage (SAH) occurring in up to half of successfully treated SAHs and is responsible for 20% of deaths and serious neurological deficit (8-10); and is still of unclear aetiology (11). Its incidence is sudden and usually presents within the first 4-9 days after SAH without any preceding signs or symptoms (12). Diagnosis is usually confirmed via the gold standard invasive CT angiography after which, various treatment approaches are initiated to salvage adequate cerebral perfusion (13). Several efforts have been made to identify potential factors that may be used for early detection of Vasospasm; however, it remains one of the major challenges in Neuro-intensive care (14). Recent trials include the use of continuous EEG monitoring, measuring CSF glutamate and serum S100 Biomarkers, regular Transcranial Doppler (TCD) ultrasonography imaging, or Motor Evoked Potentials (13, 15-17); none of which proved significant and practical enough for their application.

Fluctuations in Blood Pressure (BP) following SAH have been reported in early studies rendering them a candidate for possible detection of Vasospasm (1). A recent German study (2), targeted specifically at this association, reported spontaneous changes in BP as early as day 4 post-operation to be correlated with the incidence of vasospasm. Arterial BP is a routine measurement in all post-operative SAH patients, the presence of correlation with Vasospasm may suggest a non-invasive, easily accessible, and cost-effective strategy to sensitise healthcare and guide prophylactic measures. Detecting specific changes in either Systolic, Diastolic or Mean Arterial Pressure may also aid in the understanding of the underlying pathophysiology and development of new treatments (2).

Objectives

This systematic review seeks to condense and appraise existing literature on the relationship between BP and Cerebral Vasospasm following SAH through the following objectives:

1. Determine the trends in BP after SAH with regards to SBP, DBP, and MAP.
2. Analyse current evidence on the relationship of BP to the incidence of Cerebral Vasospasm

Methodology

Search Strategy

On the 3rd of January 2020, electronic searches were conducted in EBSCO MEDLINE and PubMed to retrieve all relevant articles that will achieve the objectives of this review.

The following search criteria was finalised:

- In EBSCO MEDLINE (https://www.ebsco.com/products/research-databases/medline) with the aid of MeSH Terms:
    I. Blood Pressure
    (MM "Blood Pressure+") OR (MM "Arterial Pressure") OR (MM "Venous Pressure+") [All Fields]
    AND
    II. Subarachnoid Haemorrhage
    (MM "Subarachnoid Hemorrhage+") OR (MM "Subarachnoid Hemorrhage, Traumatic") [All Fields]

  Initial search yielded 94 articles. 74 articles were obtained after application of language and human subject filters.

- In PubMed (https://pubmed.ncbi.nlm.nih.gov/) with the aid of MeSH Terms:
    III. Blood Pressure
    Blood Pressure[Title/Abstract]
    AND

IV. Subarachnoid Haemorrhage Subarachnoid *morrhage[Title/Abstract] OR "subarachnoid hemorrhage"[MeSH Terms]

Initial search yielded 674 articles. 472 articles were obtained after application of language and human subject filters.

Equations generated by EBSCO MEDLINE and PubMed are found in Appendix A.

Selection Criteria
Table 2 lists the inclusion and exclusion criteria applied in this review.

Selection Process
Due to the limited number of results, the timeframe for the published articles was not restrained to avail all the relevant literature possible.

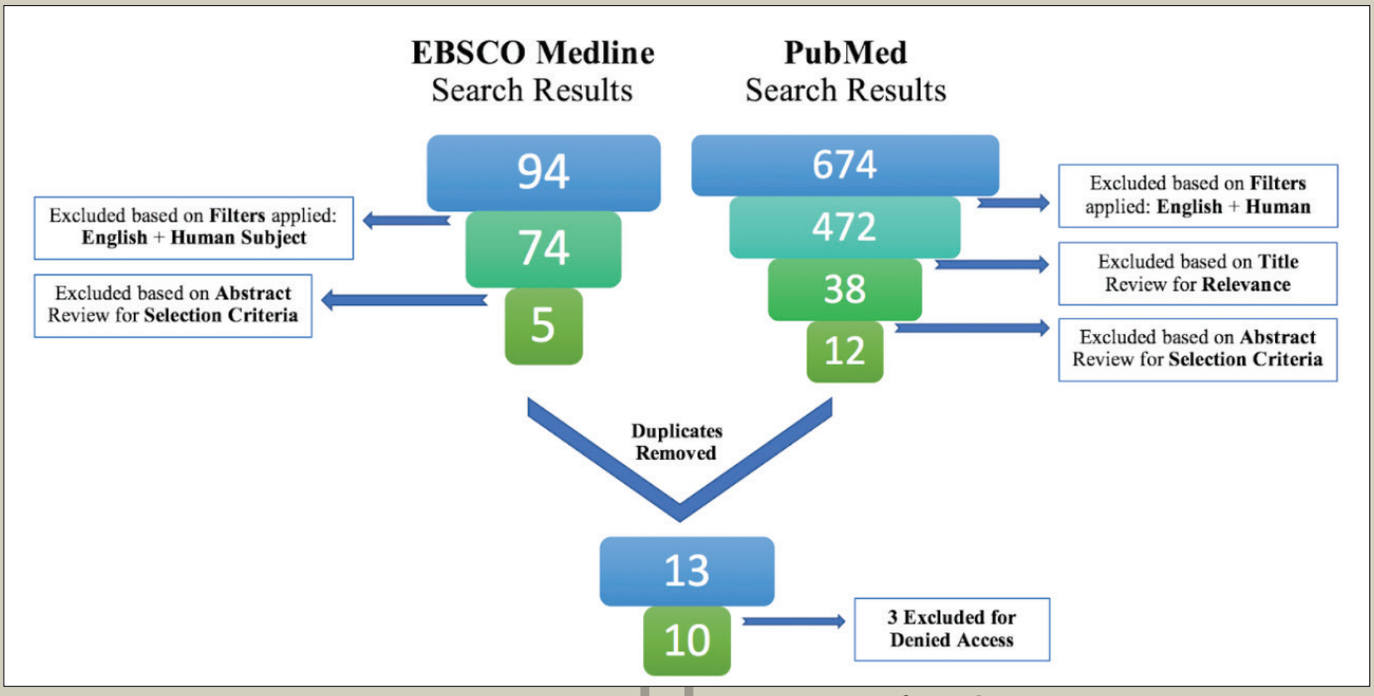
Articles involving drug trials were excluded to avoid the effect of drug therapy on the BP trend observed. Articles that merely analysed BP within the first 24 hours were excluded to avoid unnecessary analysis not aiding Vasospasm prediction; along the same basis, articles that initiated analysis more than 4 days after SAH were deemed inaccurate for this review as uncertainty will retain on whether Vasospasm has already onset.

Thorough screening eventually yielded 5 articles from Medline and 12 from PubMed; upon removal of duplicates, 13 articles were drawn. Three of the resulting articles were denied access and required paid subscriptions, yielding a total of 10 articles for analysis.

Critical appraisal and analysis
The 10 articles were then thoroughly read and critically appraised using the CASP Cohort Study checklist (20). Although the tool does not provide quantitative analysis to papers' validity, its use was preferred as it avails the option to annotate and encourage reasoning for each analytic answer to the paper's accuracy and findings. It is also appropriate for cohort studies given that all our search results have a cohort study design.
Table (4) found in Appendix B summarizes the Yes/No answers to the CASP checklist for the 10 reviewed articles.

Inclusion Criteria	Exclusion Criteria
Studied SAH patients	Involved drug trials
Recorded BP measurements of either SBP, DBP or MAP as a variable	Evaluated unconscious/comatose/vegetative patients
Conducted on human population	Analysed BP before the incidence of SAH
Available in English	Analysed ≤24 hrs of BP after SAH
	Started BP analysis > 4 days after SAH onset
	Not accessible even through the UCC portal
	Studies conducted on animal populations

Table 2: Inclusion and Exclusion Criteria



Data of daily BP measurements provided by 3 studies was extracted and inputted into an Excel spreadsheet for production of a collated line graph and to facilitate visual and mathematical analysis of BP trends (refer to Figure 2 in Section 4.2).

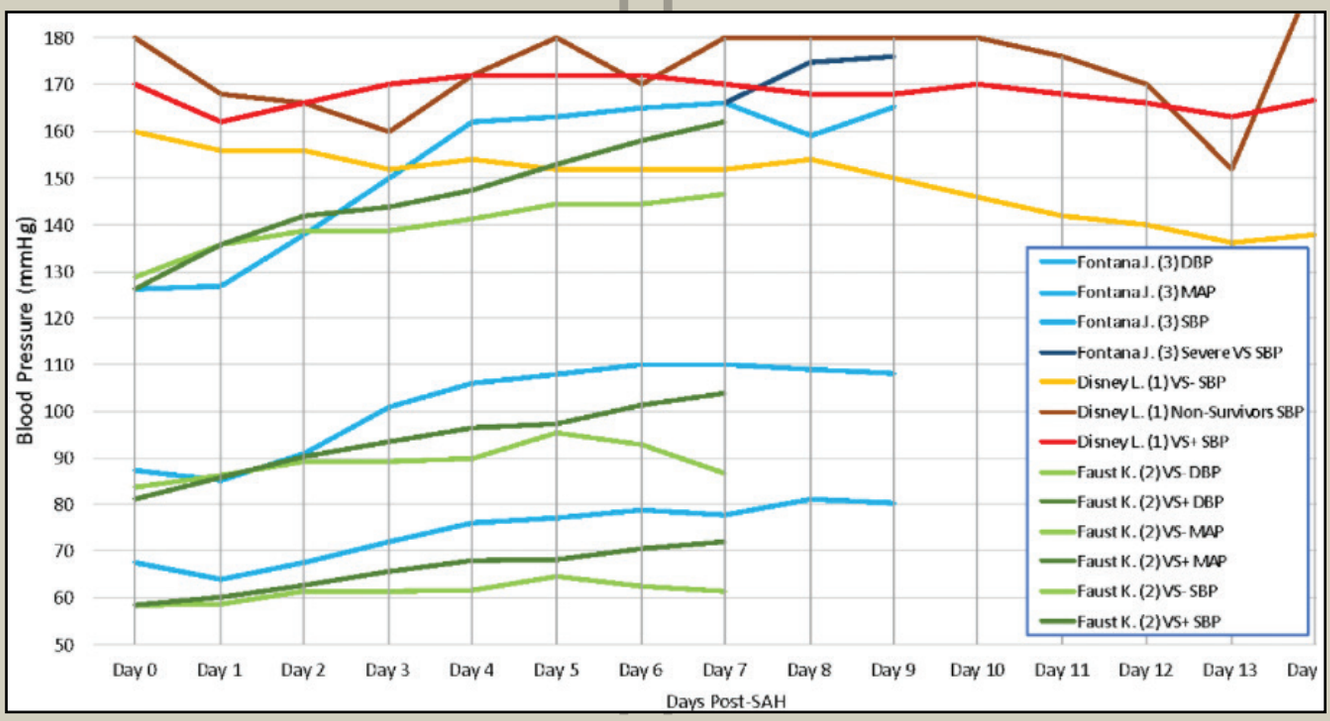
Results

Summary table of results

Refer to Appendix C

Presentation of results

All 10 articles analysed BP trends after SAH to an extent: 3 of which provided daily readings (extrapolated into the results line graphs, Fig.2 (1-3)), 2 emphasised specific changes in SBP (5) or MAP (21) in terms of magnitude and frequency, and 7 attempted to analyse BP in terms of prediction of Cerebral Vasospasm (1-7). Analysis and results of 2 studies focused on presenting the complexity, variability and Time-Frequency analysis of BP and did not provide absolute BP values (18, 19); hence, they were not very specific to the objective of



Blood pressure trends following SAH

The majority (62.5%) of the studies reported rises in SBP and an equivalent reported MAP but only a minority (25%) reported DBP trends. Each variable differs significantly between the studies with SBP ranging between 126.04mmHg (2) and 180mmHg (1) on Day 0 (day of SAH), MAP between 81.25mmHg (2) and 122.824mmHg (4), and DBP between 58.32mmHg (2) and 67.76mmHg (3) (refer to Fig.2).

Fontana et al. (3) and Faust et al. (2) agree that a gradual rise is seen amongst the BP variables as the days progress after SAH, while Disney et al. (1) depict that an initial fall is seen in Day 1 followed by a gradual rise to Day 8 and a subsequent gradual fall afterwards. The plateau seen between Day 4 and 7 is consistent with the findings of Teping et al. (21) where Endogenous Persistent Hypertension of MAP > 117.16 (± 9.92) mmHg was noted at a greater frequency in Phase 2 of their study period (Days 4-14). Tabuchi et al. (5), on the other hand, annotated spontaneous falls in SBP defined as drops of > 40 mmHg mostly seen in Days 2-5 and Days 7-17; both of which are inconsistent with the line graphs illustrated.

Blood pressure and cerebral vasospasm prediction

The correlation between BP and Cerebral Vasospasm was depicted in all but one study (21) which analysed Delayed Cerebral Ischaemia without specifying if associated to Vasospasm or not. One third of the studies (1-3) agree that a significant steeper rise in SBP is seen in Vasospasm patients. This is seen as early as Day 3 by Disney et al. (1), who also emphasise that the increase in BP precedes the onset of clinical symptoms; Day 6 (SBP) and Day 4 (MAP) by Faust et al. (2), who also claim that >20% rise in MAP provides a Positive Predictive Value (PPV) of 86%. Fontana et al. (3) illustrated a secondary Norepinephrine (NE) independent rise in SBP seen in patients with severe global Vasospasm as shown between Days 8-9 in Figure 2.

In contrast, another third of these studies demonstrated a drop in BP as a predictor of vasospasm (4-6). Yarlagadda et al. (6) reported that a drop of SBP below 130 mmHg in Day 5 post-SAH is associated with death (OR=6.7) which coincides within the "clinical window" of Cerebral Vasospasm. Tabuchi et al. (5) evoke that 70.4% of the spontaneous falls in SBP recorded were significantly associated with symptomatic Vasospasm, 22% of which occurred before the incidence. Roederer et al. (4), however, only elicit the association of MAP on Day 1 post-SAH and claim that MAP of 107.524mmHg (CI=2.99-27.72) has a better PPV and sensitivity than TCD imaging in predicting Vasospasm. Placek et al. (18) and Soehle (19) report opposing results arguing an increase or decrease in complexity of BP during Vasospasm. In contrast to all of the other studies, Kirkness et al. (7) concluded that MAP (both level and variability) measured over 4 days has no significant relation to Vasospasm.

Discussion

Blood pressure trends following SAH

Trends in BP following SAH have been elicited across clinical and physiological studies since the early 1980s and as shown by this review, BP fluctuations are inevitable and vary despite rigorous control (1). In this discussion, the time period following SAH is divided into 2 phases as done by Teping et al. (21) to facilitate analysis: Phase 1 (Day 0-3), and Phase 2 (Days 3-14). A conflict is seen from Day 0 of Phase 1 between the results of Disney et al. (1) and the results of Fontana et al. (3) and Faust et al. (2) (Fig.2) where the former claim a significantly higher SBP that remains at a mean SBP of (156± 3.02) mmHg throughout the first phase. The 3 eventually conjoin at the start of Phase 2 with a noticeable steeper rise in Fontana et al. (3).

Given the limitations of the study by Disney et al. (1) in neglecting vital confounding consideration such as Vasopressor Therapy, application of Nimodipine, history of hypertension, sedation level etc. and the fact that only 24% of the proposed sample had available records

gives a potential for sampling and confounding bias. It is also worth noting the age of the study (1989) which although limits its available technology, sets a basis for all present studies in SAH and BP association.

The steeper and more pronounced rise between Days 1-5 seen in Fontana et al. (3) can be explained by its strict yet plausible control in its study design; it is the only prospective study and controlled for all aforementioned confounding including the restriction of standard Nimodipine prophylaxis (22). As one of the most recent available research, with its multi-level quality assurance in terms of comprehensive measure of exposure and outcome and analytical testing, its relevance and viability are greatly strengthened. The only limitations encountered were the relatively small sample and the undisclosed mode of treatment.

Despite the relatively less pronounced rise seen with Faust et al. (2), it provides a more accurate reflection of the actual ICU setting, where prophylactic Nimodipine is applied and various covariables matched for to ensure reliability. The study provides promising results in predicting Vasospasm as will be seen in the next section. The sample was larger and included patients from both surgical and endovascular SAH treatment, providing significant level of evidence. Both studies (2,3) provide substantial evidence for a relatively normotensive BP on Day 0 that rises within the next few days to reach a plateau of (154.08±10.79) mmHg between Days 4-8. Disney et al. (1) also remains within proximal statistical range throughout this period.

Spontaneous blood pressure increases (SBI) as well as prolonged Endogenous Persistent increases (EPI) are seen by Teping et al. (21) - detected across all phases but predominantly during Phase 2. The quality assurance strategies with regards to visual cross-checking for artefacts, frequent exposure measure, comprehensive confounding analysis and evidential exclusion criteria avail a significant result that cannot be overlooked. In addition to its alignment to the results above in terms of temporal distribution of BP rises, Teping et al. (21) evoke a disparity in BP regulation that was merely hypothesised in other studies (1-3); The difference in timing seen in SBI and EPI suggests that the initial response to demand and the capacity to sustain this response are not necessarily interchangeable. On the contrary, sudden falls (rather than rises) in SBP are depicted by Tabuchi et al. (5) predominantly in Phase 2. However, considering that only 41.6% of their sample experienced these falls and given the old sample set (1987-1996) relative to the date of the study (2006), the low prevalence and historical changes in management and recording of data provide an unavoidable level of inaccuracy. It is also worth noting that the biological plausibility of the study is based on non-human experiments. Nevertheless, since the hypotensive effect is claimed to be seen even after aggressive volume resuscitation, analysis of falls is recommended to be in consideration in future research.

Blood pressure and cerebral vasospasm prediction

With regards to Cerebral Vasospasm prediction, promising results are seen by Disney et al. (1), Faust et al. (2) and Fontana et al. (3); a statistically significant rise in SBP is associated with Vasospasm in all three. Faust et al. (2) studied a German sample of 98 patients and was particularly targeted at finding the predictive value of BP changes to Vasospasm incidence. It concluded that a 20% elevation in MAP is sufficient to sensitise care into anticipating Vasospasm. However, the study was limited to retrospective analysis and matching for confounding factors, confounding randomisation in future prospective studies is recommended to increase diagnostic specificity.

A year later, Fontana et al. (3) revealed similar promising results, also in a German sample of 61 patients, with higher accuracy through eliminating most potentially influencing variables. Given the various limitations of Disney et al. (1) aforementioned, a similar significant result was still elicited, in addition to associat-

ing unstable varying BP to mortality. (refer to brown line in Fig.2)

Meanwhile, Yarlagadda et al. (6), Tabuchi et al. (5), and Roederer et al. (4) conversely display a drop in BP as a predictor of Vasospasm. Despite the high odds ratio (OR=6.7) portrayed by Yarlagadda et al. (6), it is worth mentioning that the study focused on other exposures of cardiovascular abnormalities and its measurement of outcome was not sufficiently accurate in identifying Vasospasm. For example, treatment of Vasospasm or head CT evidence of cerebral infarction are not necessarily indicative of Vasospasm as defined in this study. BP was also only measured 3 times during the 5-Day study period.

In support of this drop in pressure relationship, 22% of Tabuchi et al. (5) reported drops in BP happened prior to the incidence of symptomatic vasospasm, however, only 5.5% are stated by the study to be within 6 hrs and considered causative. Nonetheless, to our analysis, a significant association is considered whether causative or not. However, the aforementioned critical analysis in the accuracy of this study must be noted. (refer to the last paragraph of Section 5.1)

A relatively new study (2014) analysing the viability of using automated physiologic data to predict Vasospasm in the ICU setting also supported the drop in pressure hypothesis and associated an MAP of 107.524mmHg on Day 1 to Vasospasm compared to 122.874mmHg in Non-Vasospasm patients (4). The study had extensive analytic statistical and validation techniques and an apt consideration of confounding variables. However, the 3-day study period was insufficient, only high-grade patients were recruited and no plausible physiologic evidence is available for the relationship of Vasospasm with BP on first day following SAH. Kirkness et al. (7) had similar MAP values for a similar study period (4 Days) yet concluded that there is no significance between MAP and Vasospasm. This is in agreement to the current available evidence aforementioned that Vasospasm is usually onset Day 4 post-SAH (12).

Limitations of study

This review was limited by the number of available literature examining the trends of BP following SAH. Denied access to 3 additional studies found may have restricted vital evidence. The use of only 2 databases also provides possibility of non-accessed literature.

Conclusion

Despite the inconsistent absolute values of BP variables, it is rational to conclude that a biphasic trend is expected following SAH with an initial gradual rise during the first 4 days followed by a sustained hypertensive plateau fluctuating depending on severity and prognosis. With regards to Cerebral Vasospasm, considerable conflict is depicted in literature on whether spontaneous rises or falls in BP are associated with Vasospasm incidence; with the former showing greater significance in recent literature. Nevertheless, the presence of a correlation and potential prediction is almost ascertained; further analysis of such beneficial predictive potential is hence required for further advancement in Vasospasm and Neuro-Cardiogenic care.

Appendix A

EBSCO MEDLINE Generated Equation

((MM "Blood Pressure+") OR (MM "Arterial Pressure") OR (MM "Venous Pressure+")) AND ((MM "Subarachnoid Hemorrhage+") OR (MM "Subarachnoid Hemorrhage, Traumatic"))

PubMed Generated Equation

(Blood Pressure[Title/Abstract] AND (Subarachnoid *morrhage[Title/Abstract] OR "subarachnoid hemorrhage"[MeSH Terms]))

Appendix B

CASP Checklist Question (20)	Disney L. *et al.*	Faust K. *et al.*	Fontana J. *et al.*	Kirkness C.J. *et al.*	Placek M. *et al.*	Roederer A. *et al.*	Soehle M. *et al.*	Tabuchi S. *et al.*	Teping F. *et al.*	Yarlagadda S. *et al.*
1. Did the study address a clearly focused issue?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2. Was the cohort recruited in an acceptable way?	CT	Y	Y	CT	Y	N*[4]	Y	Y	Y	Y
3. Was the exposure accurately measured to minimise bias?	Y	Y	Y	Y	CT	Y	Y	Y	Y	CT
4. Was the outcome accurately measured to minimise bias?	Y	Y	Y	CT*[1]	CT	Y	CT	Y*[5]	Y	N
5. (a) Have the authors identified all important confounding factors?	N	Y	Y	Y	CT	Y	Y	Y	Y	Y
5. (b) Have they taken account of the confounding factors in the design and/or analysis?	N	Y	Y	Y	Y	CT	Y	CT	Y	Y
6. (a) Was the follow up of subjects complete enough?	N	Y	Y	Y	Y*[3]	Y	Y	Y	Y	Y
6. (b) Was the follow up of subjects long enough?	CT	Y	Y	N	CT	N	CT	Y	Y	N
7. What are the results of this study?	*Refer to Table (3): SUMMARY OF RESULTS*									
11. Do the results of this study fit with other available evidence?	Y	Y	Y	Y	CT	N	Y	Y*[6]	Y	N
12. What are the implications of this study for practice?	*Refer to Table (3): SUMMARY OF RESULTS*									

Y : Yes
N : No
CT : Can't Tell

*[1]Qs maybe be tailored to Parent Study
*[2]Not all results believed
*[4]Only High-grade patients recruited
*[5]Clearly defined; however, not Gold standard measure
*[6]Evidence from Rat studies

Other reasons for CT and N answers are explained in the Limitations section of the Summary of Results Table

Appendix C

Table 3: SUMMARY OF RESULTS

Author (Year), Location, Title	Study Design, Sample Size / Selection	Methods	Key Findings	Strengths / Limitations	Future Research
Disney L. *et al.* (1989) *Alberta, Canada* **Trends in Blood Pressure, Osmolality and Electrolytes after Subarachnoid Hemorrhage from Aneurysms (1)**	Retrospective Cohort study N= 173 SAH Patients admitted to University of Alberta Hospitals or Royal Alexandra Hospital **Inclusion:** • 1971 – early 1987 • ≥ 2 days of Vital signs and Biochemical data available	**Exposure:** **BP** from Patients' charts (not every day available!) **Outcome:** **Mortality** – Death in Hospital **Vasospasm** – Delayed Neurological deterioration occurring > 4 days after SAH and associated with Angiographic Vasospasm	**BP Trend:** • Highest mean SBP on Day 0 = 163torr • Fell on Day 1, gradual rise to Day 8 the fell again • Considerable variation of SBP over time for Non-survivors **Vasospasm:** • Days 3-14: significantly higher SBP in Vasospasm group • Low BP = ½ incidence of VS • Difference increases progressively overtime • BP rise before Clinical onset of VS • Difference emphasized when categorized in comparison to Highest SBP on that day.	**Strengths:** • Biologically plausible evidence • Temporality established • Overall large sample size • Clearly defined outcome • Reasonable variation of sample (Gender, Age, Hunt & Hess grade on admission) **Limitations:** • No confounding factors considered • Not all days of data available • Only Surgical treatment • 173 patients from 721 had recorded data – sampling bias	

Table 3: SUMMARY OF RESULTS

Author (Year), Location,	Study Design, Sample Size	Methods	Key Findings	Strengths / Limitations	Future Research
Faust K. *et al.* (2014) *Berlin, Germany* **Blood pressure changes after aneurysmal subarachnoid haemorrhage and their relationship to cerebral vasospasm and clinical outcome (2)**	Retrospective Cohort study N= 98 **Inclusion:** • Aneurysmal SAH **Exclusion:** • No Angiogram to confirm diagnosis • Initial presentation of VS • No detected aneurysm as source of bleed • Received delayed aneurysmal disabling	**Exposure:** **BP** from Patients' charts For 8 Days **Outcome:** **Vasospasm** –33% narrowing of Cerebral vessels via Catheter Angiography on Day 7-9 Earlier if: • Delayed neurological deterioration not attributable to another source • TCD flow elevation (MCA>120cm/s, ΔMCA velocity 24hr>50, Lindegaard index*>3) **Clinical Outcome** – Glasgow Clinical Outcome Scale ** Lindegaard index: the ratio between the mean flow velocity in the median cerebral artery and the mean flow velocity in the internal carotid artery*	**BP Trend:** • Daily data of DBP, MAP, SBP of available **Vasospasm:** • Days 1-8 = VS+ MAP ↑ 28% VS- MAP ↑ 3.5% • Statistical difference in MAP & DBP between VS+ & VS- on Day 4 • Statistical difference in SBP on Day 6 • Predominance in changes of DBP • >20% spontaneous elevation in MAP might sensitize ICU for VS • Result unaffected by History of Hypertension, Age, Gender, Treatment modality • SAH severity (WFNS) did not correlate with BP	**Strengths:** • Confounding factors matched • Reflect real ICU situation • Temporality established • Supported by physiological evidence • Good sample size • Clearly defined outcome **Limitations:** • Not sufficient variation with regards to age • Regular Nimodipine may affect BP trend	Future Prospective studies randomizing variables (instead of matching)

Fontana J. *et al.* (2015) *Bochum, Germany* **The spontaneous arterial blood pressure rise after aneurysmal subarachnoid haemorrhage – A biphasic phenomenon (3)**	Prospective Cohort study N= 61 **Inclusion:** • Aneurysmal SAH • 18< Age <85 • Saccular aneurysm by DSA with chronologically defined onset **Exclusion:** • Non-aneurysmal SAH • Onset >24hrs • No or only thin clot on baseline CT (>20mm length)	**Exposure:** **BP** – Continuously monitored by intra-arterial catheter SBP, DBP & MAP for 9 Days **Outcome:** **Vasospasm** –DSA on Day 8±2 quantified as None, Mild, Moderate or Severe via DSA by measuring diameter relative to baseline angiogram on admission Angiography on Day 7-9 **Clinical Outcome** – modified Rankin Scale, National Institute of Health Stroke Scale, Glasgow Outcome Scale Extended at Discharge	**BP Trend:** • Daily data of DBP, MAP, SBP of available • Significant rise in all ($P<0.0001$) • Steepest rise between Days 1-5 **Vasospasm:** • Isolated secondary rise of SBP in severe VS global on Day 8-9 • Mean vessel diameter reduction = -21.3 (±23.30)% • Global VS significantly related to daily rise of DBP, SBP and strongly MAP • Steeper rise in patients with History of Hypertension • No significance of BP ad Gender, Aneurysm Location, NE application • Propofol had significant inhibitory influence on SBP • SBP rise sig. correlation to SAH severity by Hijdra score	**Strengths:** • Prospective • Confounding factors dissected including Nimodipine use • Continuous exposure monitoring • Multi-level quality checks • Outcome measured for inter-observer variability • Outcome sub-quantified relative to baseline of individual • Plausibility based on physiological evidence **Limitations:** • Small sample size • Most treated by Surgical clipping • Influence of NE doses cannot eventually be fully excluded	
Kirkness C.J. *et al.* (2009) *Seattle, USA* **Intracranial and Blood Pressure Variability and Long-Term Outcome After Aneurysmal Subarachnoid Hemorrhage (7)**	Descriptive correlational analysis of physiological data gathered as part of a Randomized Clinical Trial N= 90 **Inclusion:** • Age ≥16 • Enrolled over a 2 year period	**Exposure:** **BP** – Continuously monitored by intra-arterial catheter connected to fluid-filled pressure transducers for 4 Days saved as 5-second means Variability calculated on 4 timescales: 5sec, 5min, 1hr, 2 hrs **Outcome:** **Vasospasm** – Defined by TCD criteria or other **Clinical Outcome** – trained interviewers using Glasgow Outcome Scale Extended 6 months after discharge	Faster variability correlates to better outcome **BP Trend:** • Avg. MAP over 4 days = (103.2±10.7)mmHg **Vasospasm:** • No significant association between MAP Level & variability and VS • Higher MAP level over 4 days associated with sig. lower odds of favourable outcome • No association between variability and Aneurysm location • Age inversely correlated with MAP • Women had greater 24hr MAP variability • MAP significantly correlated with anxiolytic, sedative, hypnotic dose (OR=0.2; $p=0.02$) & Corticosteroid dose (OR=0.39; $p<0.001$) • MAP 5sec variability significantly correlated with Antiarrhythmic, diuretic, vasodilator dose	**Strengths:** • Confounding factors analysed with statistical tests • Clearly explained method of exposure measurement **Limitations:** • Gender ratio imbalance • Unclear definition VS outcome • Interview questions accustomed to parent study	

Literature Reviews

Placek M. *et al.* (2015) *Cambridge, UK* **Complexity of Cerebral Blood Flow Velocity and Arterial Blood Pressure in Subarachnoid Hemorrhage Using Time-Frequency Analysis (18)**	Retrospective Cohort study N= 31 **Inclusion:** • Aneurysmal SAH • Admitted to Neuro Critical Care Unit of Addenbrooke's Hospital • Daily TCD monitoring	**Exposure:** **BP** – measured invasively by radial artery line Recorded simultaneously every 1 or 2 days for 20mins at a sampling frequency of 50Hz **Outcome:** **Vasospasm** • TCD criteria: ○ Mean FV >120cm/s ○ Lindegaard ratio >3	**Vasospasm:** • Onset of VS= 9±4 days • VS did NOT affect mean Time-Frequency Distribution measures of complexity of ABP • Reduction in complexity of ABP in early days after SAH • Gradual fall in ABP complexity before VS and rise during VS (p=0.002) • May serve as Early warning index of narrowing of cerebral arteries	**Strengths:** • Spatial and Temporal comparison of VS • Strong and Multivariate statistical analysis **Limitations:** • Analysis of study focused on time-frequency distribution and BP complexity and did not provide raw absolute BP data. • Gold standard CT not used • Small sample size • No VS- control group • No sufficient Confounding control	Whether analysis of complexity of CBFV and ABP with cerebral autoregulation assessment using Time-Frequency analysis can advance prediction of DCI
Roederer A. *et al.* (2014) *Philadelphia, USA* **Prediction of Significant Vasospasm in Aneurysmal Subarachnoid Hemorrhage Using Automated Data (4)**	Retrospective Cohort study N= 81 **Inclusion:** • Aneurysmal SAH • 2001-2011 • Fisher Grade 3 or 4 **Exclusion:** • Delayed presentation >48hrs • Early VS (during first 2 days)	**Exposure:** **BP** – Continuously monitored by arterial lines for 3 Days **Outcome:** **Vasospasm** • Serial neurological exams • Daily TCD studies • Monitored every 1-3hrs for headache or clinical deterioration • Other diagnostic tests such as CT perfusion, Xenon CT, MR perfusion, cEEG available to help	**Vasospasm:** • 43.2% of sample developed VS • MAP on Day 1 VS+= 107.524mmHg VS- = 122.874 mmHg (p=0.018; CI 2.99-27.72) • Better PPV & Sensitivity than TCD • All automated data variables measured deemed significant with VS (p<0.05) except CSF output	**Strengths:** • Patients well matched for clinical features • Different statistical & validation techniques for quality assurance • Useful as early warning **Limitations:** • Many exposure variables lead to reduced focus on MAP • Only high-grade patients – sample bias • Does not indicate anything about underlying cause • Timespan of 10 yrs – risk of historical bias • Lack of temporality	Exploration of tests to detect intellectual impairment with normal MMSE scores

Soehle M. *et al.* (2008) *Cambridge, UK* **Variability and fractal analysis of middle cerebral artery blood flow velocity and arterial blood pressure in subarachnoid haemorrhage (19)**	Retrospective Cohort study N= 31 **Inclusion:** • Aneurysmal SAH • Admitted to Neuro Critical Care Unit of Addenbrooke's Hospital	**Exposure:** **BP** – measured invasively by radial artery line Recorded simultaneously every other day for 20mins at a sampling frequency of 50Hz **Outcome:** **Vasospasm** • TCD criteria: ○ Mean FV >120cm/s ○ Lindegaard ratio >3 **Clinical Outcome** – Glasgow Outcome Scale by telephone interview 1 year after SAH	**BP Trend:** • Considerable amount of fluctuations in both FV & ABP after SAH • Variability more pronounced in FV **Vasospasm:** • Variability reduced in VS • High GOS (more favourable outcome) correlated with high standard deviation of ABP ($p<0.05$) • Decomplexification theory of illness may apply to SAH too	**Strengths:** • Blinded investigator for outcome • Temporal comparison of VS • Visual inspection for artefacts • Good analytic control for confounding **Limitations:** • Analysis of study focused on FV and BP variability and did not provide raw absolute BP data. • Gold standard CT not used • Small sample size	
Tabuchi S. *et al.* (2006) *Yonago, Japan* **Relationship of hypotension and cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage (5)**	Retrospective Cohort study N= 125 **Inclusion:** • Aneurysmal SAH • Jan 1987 – Nov 1996 • Head CT to diagnose SAH **Exclusion:** • Barbiturate Therapy • Continued administration of Vasopressor or Antihypertensive Therapy • Brain death	**Exposure:** **BP** – SBP & DBP measured every 2hrs by nurses using Riva Rocei manometer for >2 wks Continuous BP monitoring in severe grade patients **Fall in BP**: drop of >40mmHg in SBP of any 2 consecutive measurements **Outcome:** • Head CT in all patients every week for >2 months OR when there is an acute change **Symptomatic Vasospasm:** • Headache, confusion, disorientation, focal neurological deficit, decline in consciousness • CT scan confirm exclusion of other causes • Absence of other causes of decline e.g. electrolyte imbalance, hypoxia, seizure	**BP Trend:** • 41.6% experienced fall in BP at least once **Vasospasm:** • 54.4% of all patients experienced Symptomatic VS • Hypodense areas secondary to Delayed Cerebral Vasospasm in 48.1% of falls in BP • 70.4% of Falls in BP correlated to VS • 22% before Symptomatic VS • Only 5.5% within 6hrs of Symptomatic VS • Effect still seen after aggressive volume resuscitation • Falls in BP significantly higher in older patients, poor WFNS grade on admission • Falls in BP NOT related to gender, History of Hypertension, Aneurysm location, mode of treatment	**Strengths:** • Clearly defined outcome • Wide confounding analysis **Limitations:** • Gold standard for VS diagnosis not used • Sample is from a long period and relatively old to study – historical bias • Plausible evidence is of non-human experiments	Further investigation to characterize mechanisms & prevention of Falls in BP to understand the pathophysiology

Teping F. *et al.* (2018) *Aachen, Germany* **Spontaneous Elevation of Blood Pressure After SAH: An Epiphenomenon of Disease Severity and Demand, But Not a Surrogate for Outcome? (21)**	Retrospective Cohort study N= 115 **Inclusion:** • Aneurysmal SAH • Jan 2011 – Dec 2014 **Exclusion:** • <18 yrs or >80 yrs • Died within first 96 hrs • Confounding comorbidities (listed) • Preconditions potentially influencing BP (listed)	**Exposure:** **BP** – Electronic patient record SBP, MAP & DBP every 15 mins **Spontaneous Blood Pressure Increases (SBI)** defined as rise of 25mmHg verified over consecutive readings **Endogenous Persistent Hypertension (EPH)** defined as persistent MAP > 160mmHg for at least 3hrs for 21 Days **Outcome:** **Clinical Outcome** – Glasgow Outcome Scale at Discharge	**BP Trend:** • Avg. MAP during SBI episode = 105.68 (±10.7) mmHg • Avg. MAP during EPH episode = 117.16 (±9.92) • Most frequent during Phase 2 (Days 4-14) ($p<0.05$) • EPH during Phase 1 increase risk of DCI • EPH during Phase 2&3 reduce risk of functional DCI • Initial response to demand & ability to maintain response not interchangeable • SAH severity, Aneurysm location, treatment modality do NOT influence EPH • EPH more in older patients ($p<0.001$)	**Strengths:** • Clearly defined exposures • Confounding factors dissected from study • Graphs visually cross-checked to exclude artefacts **Limitations:** • Not all results statistically significant • Gender ratio imbalance	
Yarlagadda S. *et al.* (2006) *California, USA* **Cardiovascular Predictors of In-Patient Mortality After Subarachnoid Hemorrhage (6)**	Prospective Cohort study N= 300 **Inclusion:** • Aneurysmal SAH • Feb 1999 – Nov 2003 • Age >21 • SAH diagnosed by CT or Lumbar puncture **Exclusion:** • History of Hypertension • Cardiomyopathy • LVEF <50% • SAH caused by trauma or mycotic aneurysm	**Exposure:** **BP** – SBP recorded once on Days 0,3,5 of study **Outcome:** **Death caused by neurological deficit due to:** • SAH only • Evidence of DCI • Worsening of neurological status • Imaging evidence of vasospasm by TCD or CT Angiography • Neurointerventional treatment for VS • Head CT evidence of Cerebral infarction	**BP Trend:** • On Day 1 SBP >180 mmHg associated with increased risk of death (OR=5.6; $p=0.008$) • On Day 5 SBP<130mmHg associated with death in clinical window of VS • Cardiac abnormalities contribute to morbidity and mortality after SAH **Vasospasm:** • Hypotension during the clinical window of VS is a risk of death	**Strengths:** • Multivariate regression analysis for confounding **Limitations:** • Data only taken 3 times; low frequency of exposure • Outcome may not always be due to VS • Many exposure variables lead to reduced focus on BP	Treatments that could potentially prevent neurocardiogenic injury such as Beta blockers should be studied in the current era of SAH therapy Further research required to determine relationship between cardiac abnormalities & neurological outcome are causal in nature

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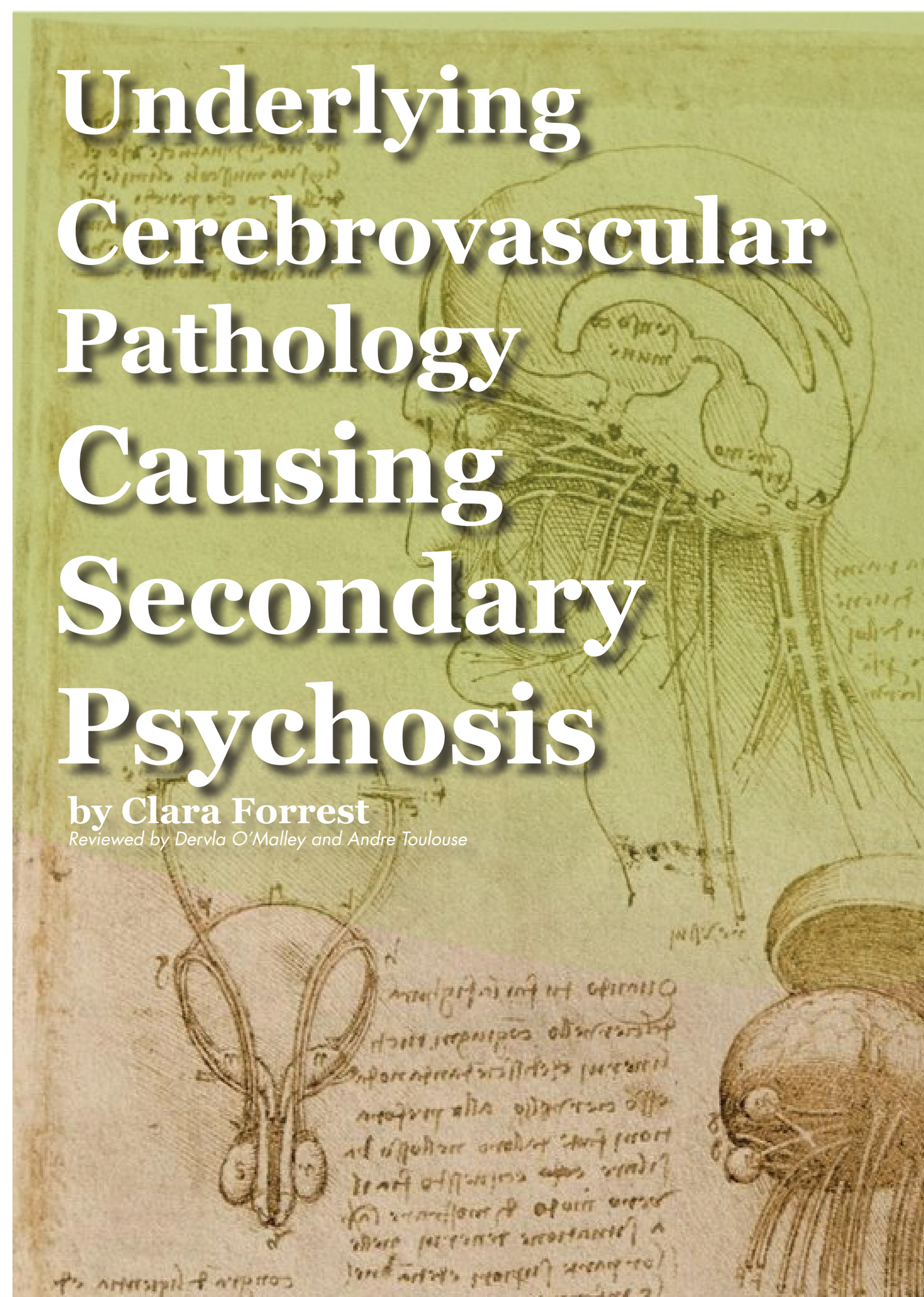
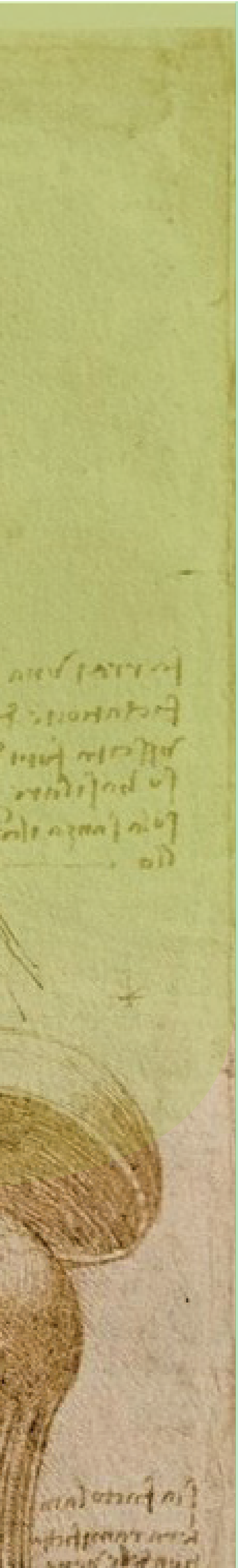
Underlying Cerebrovascular Pathology Causing Secondary Psychosis

by Clara Forrest

Reviewed by Dervla O'Malley and Andre Toulouse





Abstract

Case Background

Psychosis can be classified as primary if it is caused by a psychiatric disorder or secondary if it is due to a specific medical condition. Despite there being multiple identified causes of secondary psychosis, making such a diagnosis can prove challenging.

Case Details

This case report presents a 57-year-old male who was brought by ambulance to the emergency department following an intentional jump from a first storey window due to visual and auditory hallucinations and persecutory paranoid delusions. MRI findings on admission were consistent with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). The patient's background included an ischaemic stroke with haemorrhagic transformation five years previously. He experienced psychotic symptoms during the immediate recovery period. Prior to this he had no psychiatric history.

Discussion

Post-stroke psychosis and the condition of CADASIL are both entities that are relatively rarely described in the literature. However, this may be due to missed diagnosis and therefore not reflective of true prevalence.

Conclusion

Identifying a cause-effect relationship and establishing a diagnosis of secondary psychosis can be confounded by many factors. Nevertheless, this patient's case demonstrates the importance of considering an underlying cause, particularly when the presentation is atypical and there is a temporal relationship between the proposed medical condition and the symptoms of psychosis.

Patient Consent Obtained: Yes

Case Background

The National Institute of Mental Health describes the clinical construct of psychosis as a condition "that affects the mind, where there has been some loss of contact with reality". They report that 3% of people will experience an episode of psychosis at some time in their lives. Psychosis causes significant suffering for the patient and their family, as well as considerable social and economic consequences (1).
In the past, psychosis was classified into two groups. Organic psychoses were caused by identifiable, structural defects while functional psychoses lacked such a discrete pathology. However, this classification has limited utility today as evidence builds that functional psychoses, such as schizophrenia, now reflect some form of organic brain dysfunction. Therefore, the alternative distinguishing terms 'primary' and 'secondary' are more applicable in modern practice and this changing terminology will be forefront in the 11th International Classification of Diseases (2). They are differentiated by the fact that secondary denotes when a "pathogenic substrate" has been identified (3).
This substrate can range from autoimmune disorders, toxic substances and traumatic brain injuries to name a few. Nonetheless, establishing a cause-effect relationship can be challenging (4).
This paper presents a case of cerebrovascular pathology causing secondary psychosis. It aims to demonstrate the diagnostic challenge presented by secondary psychosis and highlight the importance of considering underlying causes of psychosis.

Case Details

Presentation

A 57-year-old male was brought in by ambulance to the accident and emergency department in the early hours of the morning following an intentional jump from a first storey window because of visual and auditory hallucinations and a persecutory paranoid delusion of a pursuant "gang". He reported seeing people coming up his stairs and onto the landing. He heard them saying to one another that they were going to harm him. The patient felt his only option was to barricade his bedroom and escape through the window. As a result, he sustained a vertebral L2 and nasal bone fracture.
At admission, a mental state examination revealed disordered thought content in the form of persistent persecutory delusions. Active second-person auditory hallucinations were also present in the form of male voices planning to hurt the patient. There was no evidence of visual hallucinations or suicidal ideation during the examination. The patient had no insight into the nature or significance of his symptoms.

Past Medical History

Five years ago, the patient suffered an ischaemic stroke with haemorrhagic transformation at the age of 52. He had no residual physical deficits, but his recovery was complicated by the development of psychotic symptoms. During this admission he was seen by liaison psychiatry for paranoid ideas, a personality change, auditory, visual and olfactory hallucinations. He had no prior psychiatric history.
Thereafter, he disengaged from services and discontinued both his antipsychotic and anticonvulsive medication. According to family member's collateral history, the stroke marked the beginning of his continued psychotic behaviour. He had not received medical attention since his stroke. He also developed an alcohol dependence consuming between five and ten units on most days of the week. He had minimal social supports and was estranged from the majority of his family.

Investigations

All investigations including electroencephalogram, paraneoplastic antibody screen, echocardiogram and carotid doppler test had normal results.
He received an MRI brain scan which showed extensive white matter signal changes throughout the corona radiata bilaterally and extending into the periventricular white matter of both frontal lobes suggesting small vessel

ischaemia. Changes in these regions of the brain have been reported in late-life onset psychosis because white matter lesions can disrupt the frontal area of the brain causing behavioural changes and symptoms that have been described as mimicking schizophrenia (5).
Evidence of a previous infarct involving the distribution of the right middle cerebral artery was also reported. There was also a small focal point of increased signal intensity in the left occipital lobe which could represent a recent lacunar-type infarct. These changes were stated to be very extensive for a patient of his age and a condition such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) was likely.

Management
Inpatient management consisted of orthopaedic treatment of the patient's fractures as well as regular assessment by the liaison psychiatry team and the commencement of anti-psychotic medication. The patient was also treated for alcohol withdrawal due to the consumption of over 10 units a day.
Figure 1. Inpatient Medication Timeline
Based on a diagnosis of secondary psychosis due to cerebrovascular disease, management was multifaceted so as to address biological, psychological and social factors.
Once the patient's mental and physical condition stabilised and improved, he was discharged. He would be reviewed regularly by the community mental health team with regards to the efficacy of the treatment as well as side-effects, adherence and physical health considering the patient had significant cerebrovascular disease and many antipsychotics can exacerbate this (6). They would also manage the reduction of his alcohol intake and a family member agreed to facilitate the patient's attendance to a local support group. Alcohol exacerbates psychotic symptoms (6), further impairs decision-making processes and increases cardiovascular risk.
With regards to social factors, the patient was provided with links to community social work services in order to apply for social welfare and adapt his current domestic situation to support his needs.

Discussion

This case report presents a 57-year-old male, with a background of ischaemic stroke with haemorrhagic transformation five years previously, who suffered an acute episode of psychosis resulting in physical injuries. MRI findings on admission were consistent with CADASIL.
Post-stroke psychosis is thought of as a rare phenomenon (3). A systematic review published last year reported that the most common post stroke psychosis was a delusional

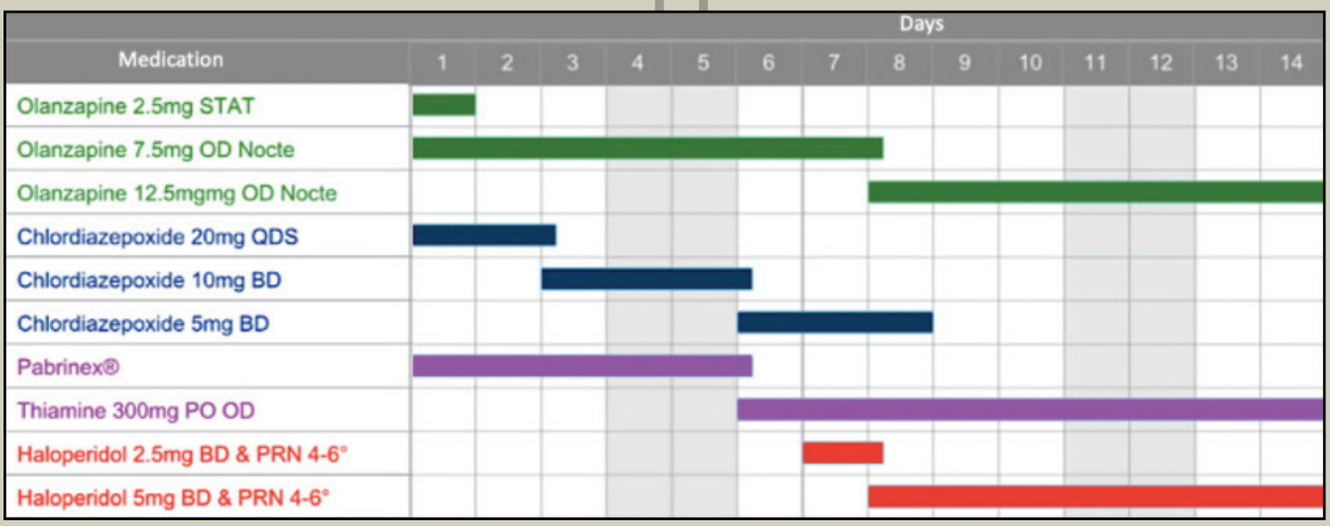


Figure 1:
Inpatient Medication Timeline

disorder which was followed by schizophrenia-like psychosis. It estimated that the prevalence of such conditions in patients post stroke is 4.86% and so perhaps is not as rare as previously imagined (7). The nature of the psychotic symptoms can be contrasted with schizophrenia as post-stroke psychosis is more likely to include visual, tactile, and olfactory hallucinations such as was the case with this patient (4).

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) was first described in the 1990s and it was "characterized, in the absence of hypertension, by recurrent subcortical ischaemic strokes, starting in early or mid-adulthood" (8). Today it is recognised as a multifaceted syndrome which can present with many signs and symptoms including migraine with aura, subcortical transient ischemic attacks, mood disorders or psychosis (9-11).

Research regarding secondary psychosis is hampered by continued debate regarding classification which leads to diagnostic difficulty. There are often numerous factors which can act synergistically and accumulate to an acute psychosis, but these can cause the boundaries between primary and secondary psychosis to blur. Both post-stroke psychosis and CADASIL are relatively uncommon in research literature but this may be attributable to difficulty in diagnosis and therefore not reflective of prevalence. However, diagnosing secondary psychosis can assist in the timely management of such patients.

Conclusion

Secondary psychosis should be considered in patients presenting with psychotic symptoms. The temporal relationship of the stroke and the symptoms of psychosis as well as the atypical nature of the symptoms were red flags that this patient's presentation was due to medical disease. Had the patient's psychiatric condition and underlying cerebrovascular disease been recognised sooner, he could have received treatment early. This emphasises the importance of increased awareness around secondary psychosis, post-stroke psychosis and CADASIL.

Acknowledgements

I wish to express my gratitude and appreciation to the patient for giving his time and effort wholeheartedly.

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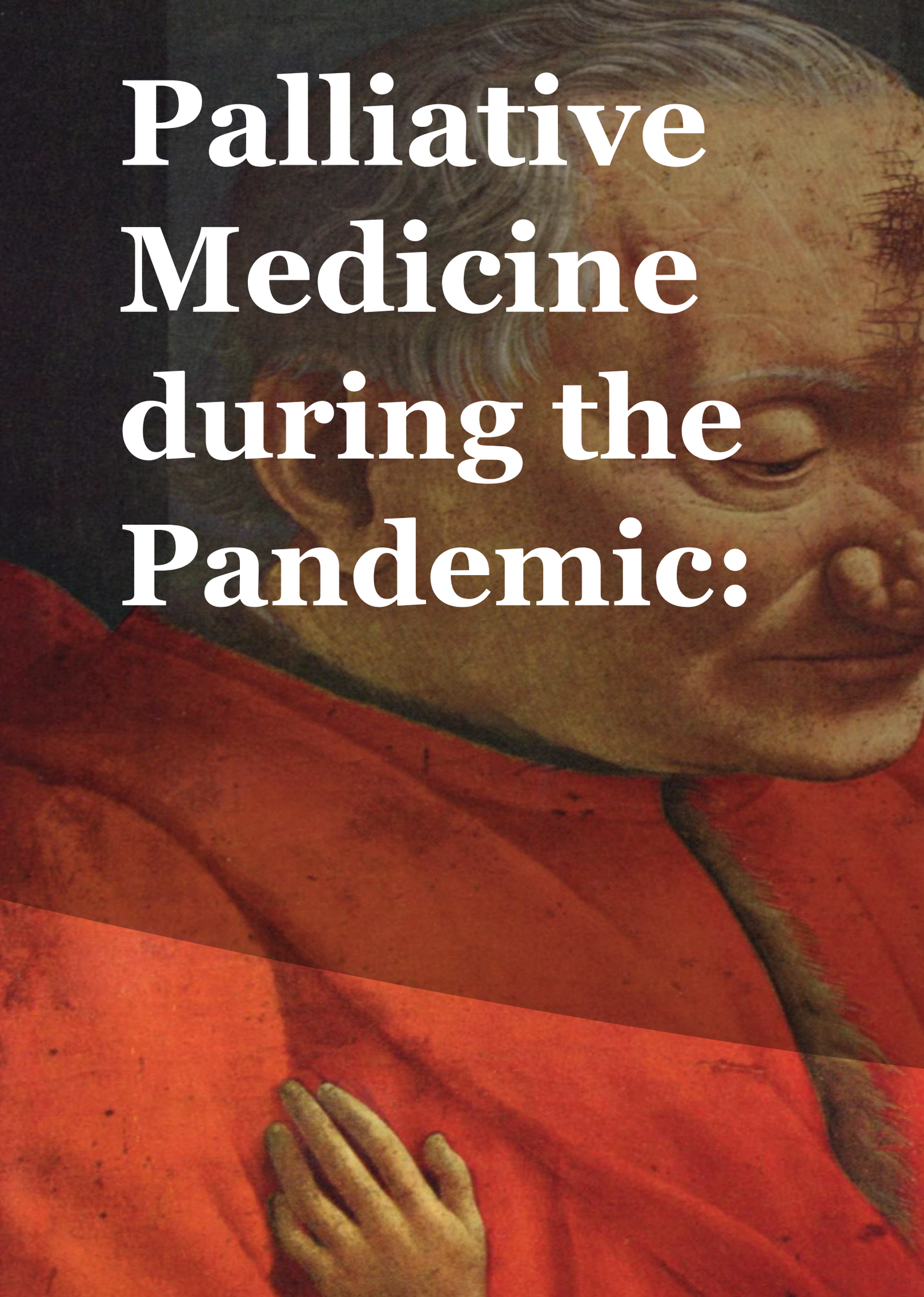
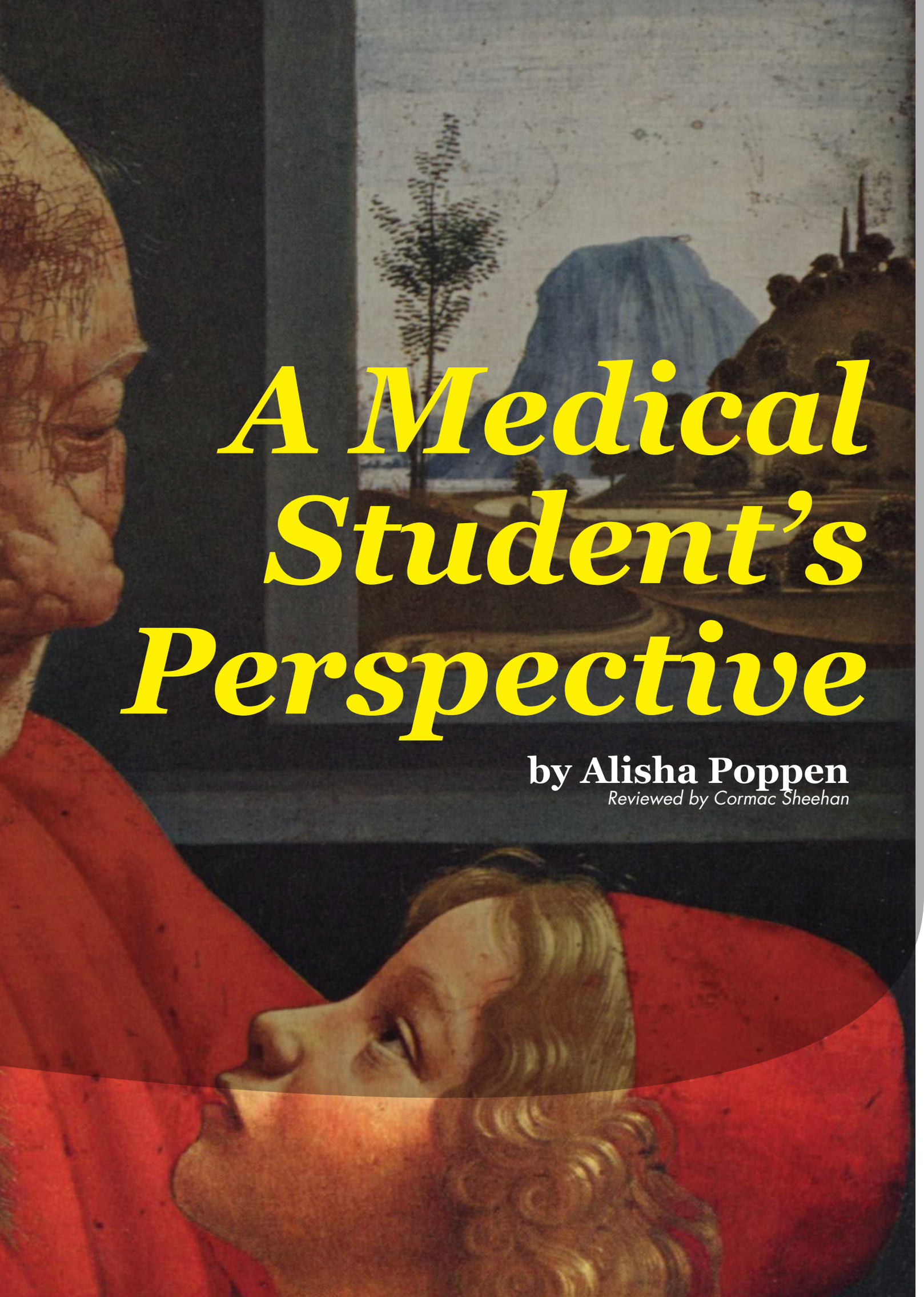


Palliative Medicine during the Pandemic:



A Medical Student's Perspective

by Alisha Poppen

Reviewed by Cormac Sheehan

Introduction

It is two weeks until Christmas. The hallways are bare. The family suites are empty. You need to buzz the receptionist to enter the building and sign in and out daily. Only visitors with appointments are allowed in. There are numerous temperature checkpoints and mask stations throughout the building. Tucked away in the outskirts of Cork City is Marymount University Hospital and Hospice. This facility with 44 beds houses the most frail, immunocompromised and terminally ill patients from all across Munster. That being said, providing palliative care was significantly affected by the challenges brought on from the ongoing global pandemic.

Effects of Pandemic Precautions

A place that was once abundant with visitors is now limited to one nominated family member per patient that can only visit during certain hours of specific days. As important as this was for infection control purposes, there were considerable impacts on the psychosocial wellbeing of these palliative patients. Speaking to many of the patients during my placement, I witnessed the low moods and feelings of isolation that permeated the ward I was assigned to. Having to spend their life's final moments away from the family and friends that encompass their support system left many individuals feeling despondent and isolated. One patient voiced her frustrations by telling me how upsetting it is to know that many people are refusing to follow public health guidelines. Consequently, the pandemic persists due to their inaction and she has to endure the impact by not having the company of her loved ones in her final days, especially during the holiday season. The patients spend most of their day alone in their suite, eagerly waiting for the two hours in the day that their designated loved one could visit. Although their medical needs were effectively treated, their emotional needs suffered. Unfortunately, the strict measures in place to protect both patients and staff came at the expense of the patient's quality of life.

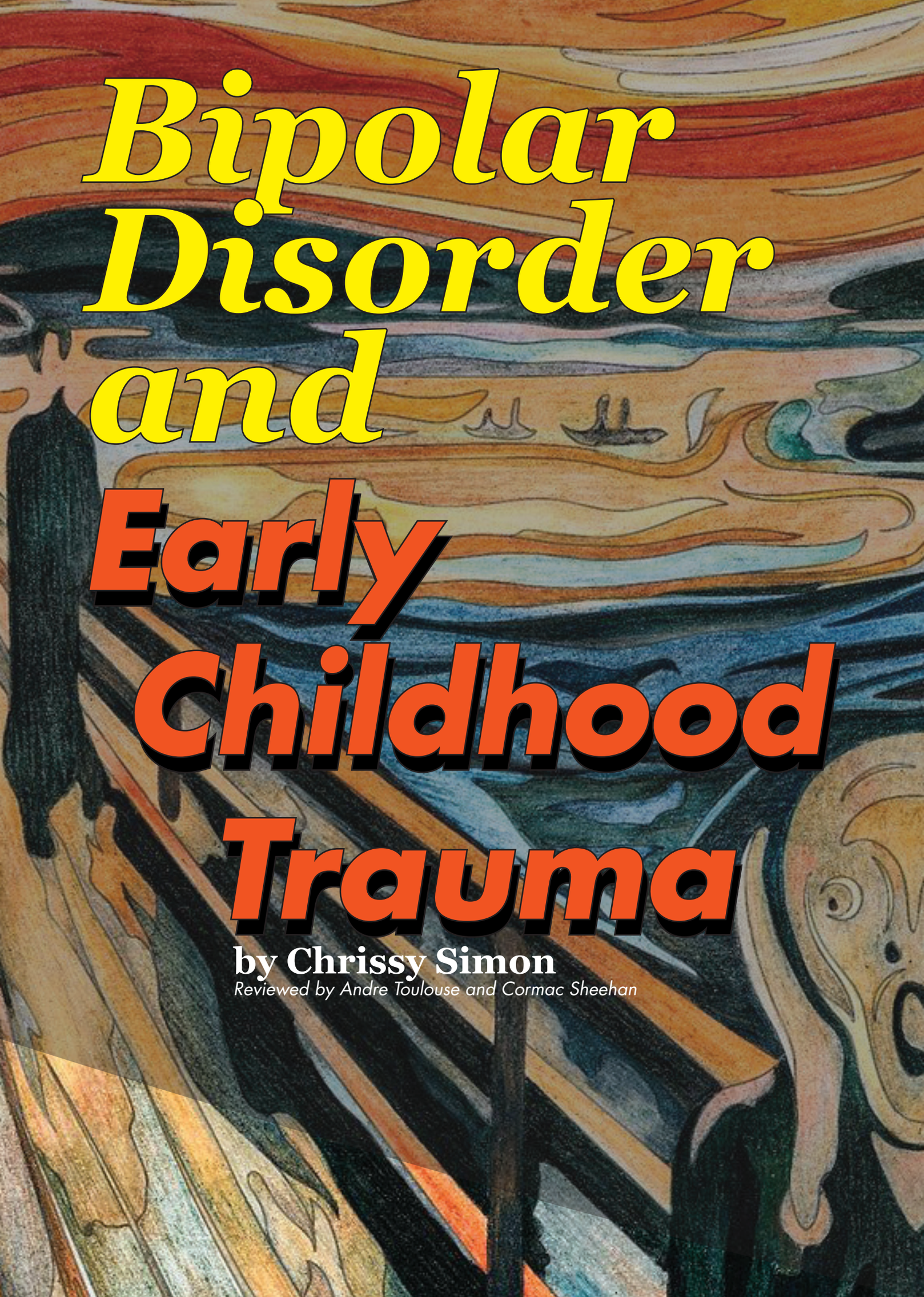
Patient-Centered Care

As a medical student, this was my first exposure to palliative care. Interestingly, there were no monitors at the bedside, the patients were not hooked up to IV bags and the nurses were not frequently checking in to record the patient's vital signs. Having only gained experience in an acute hospital setting prior to this, my mindset was always focused on diagnosis and treatment. This was not the case in palliative care, where most of the patients have a terminal diagnosis. Whether it is cancer with extensive metastasis or advanced stage Parkinson's Disease, every patient has a pathology that cannot be cured. Rather, the focus is shifted to comfort measures, pain management and holistic care. Every day began with meeting each patient and enquiring about how they are feeling, how their night was and how the team can best address their needs. Following this, adjustments are made to medications

to minimize their symptom burden and members of their multidisciplinary team pay a visit. Whether it is the physiotherapist who helps them regain their physical strength, or the chaplain who guides them spiritually, every patient determines the amount and type of care they receive.

Conclusion

This was a unique experience as it challenged the notion that the patient must listen to the doctor to recover. Instead, the doctors and allied health professionals must listen to the patient. Although their medical needs were met, their psychosocial needs remained a concern as visiting limitations were imposed due to the pandemic. This placement was not for the faint of heart. However, it was truly a masterclass in learning about empathy and understanding that quality of life is more important than length of life.



Bipolar Disorder and Early Childhood Trauma

by Chrissy Simon

Reviewed by Andre Toulouse and Cormac Sheehan

Abstract

Case Background

There is a reported 48.8 million case of bipolar disorder (BD) worldwide.16 It can also be one of the most challenging disorders to manage clinically as patients often have poor medical compliance and numerous relapses throughout their lifetime. The etiology of this illness is still poorly understood, but it is recognized to compromise both genetic and environmental factors. Regarding the latter, abuse and instability in childhood and adolescence was reported as an important area of consideration in regard to the development and prognosis of bipolar disorder.

We report here the case of a female who exemplifies the significance of early childhood experience in this disorder.

Case Presentation

Isabelle is a 21 year old, female, with a background history of bipolar disorder. She presented to the Cork University Hospital accident and emergency 2 weeks after discharge after a 4 week admission for a depressive episode. Isabelle was referred from the home-based team with an acute episode of mania and was detained involuntarily under the Mental Health Act. Her history is significant for childhood neglect, physical, emotional and sexual abuse, along with multiple foster care placements. She was managed as an inpatient with antipsychotics and a mood stabilizer before being discharged after a lengthy, arduous, admission.

Conclusion

Childhood trauma is an important consideration in BD. Therefore, practitioner awareness of the role of such trauma with regard to its etiology and prognosis is of great importance. It is also essential to the practice of preventive medicine.

Patient Consent Obtained: Yes

Case Report

Introduction

Bipolar disorder (BD) is a psychiatric illness associated with episodes of mania or hypomania and depression. The etiology of the illness has been described as being associated with the complex interplay of biopsychosocial factors. 3

BD has a poor prognosis. There is a 15% morality rate by suicide and manic relapse within 5 years is reported to be as high as 90%.1 Many patients who have the disorder also report a history of childhood trauma. In fact, it is more prevalent in BD patients than the general populace.3 Early trauma is also associated with an earlier onset of illness.4 Therefore, it is vital to understand the significance of such personal history in regard to its biopsychosocial etiology and long-term prognosis.

Case Presentation

Isabelle is a 21 year old female that presented to the emergency department with an acute manic episode. She had been discharged from the mental health unit 2 weeks prior for a depressive episode. On her last admission she was involuntarily admitted for 4 weeks.

Isabelle now re-presented with a two week history of risky behavior including late night excursions, cannabis use, and increased activity. During this time she was contacted by the outpatient home-based team after missing her routine follow-up. She was reportedly aggressive on the phone. In person they found her hostile and verbally abusive, with pressured speech, and a flight of ideas. She also believed that her family had stolen her identity and that her mother was not her real mother. Isabelle insisted that she not be called by her given name. Although an attempt to further elucidate these delusions was made, Isabelle did not want to speak further on the matter. She was involuntarily admitted under the Mental Health Act 2001.

Although Isabelle was only given a formal diagnosis of BD recently her history was extensive. Isabelle had 3 admissions within the past year. Each presentation (whether manic or depressive) was similar in nature and there was an extensive history of poor compliance. Her medications included Quetiapine, Haloperidol, Zopiclone, and Lithium. Although she had shown some success with Lithium she admitted to its discontinuation due to weight gain. Furthermore, there had always been challenges with her inpatient management as she often became volatile with staff, refused treatment, and showed an overall lack of insight into her condition. Discharge was also difficult as she reported anxiety with living independently and often preferred the security of in-patient housi ng.

Isabelle was born to an adolescent mother and absent father. She was later removed from her mother owing to neglect and physical abuse attributable to her mother's alcoholism, cocaine addiction and personal BD history. Isabelle was subsequently cared for by her grandparent until they passed. She was consequently placed in foster care where she reported emotional and physical abuse.

Isabelle described her childhood as fraught with antisocial behavior. It was because of her volatile behavior, and repeated incidents of physical altercations in school, that she was required to see a psychologist. There was some uncertainty regarding if she was diagnosed with a borderline personality disorder at his time but Isabelle disputed this and there was no formal record of diagnosis. She later left school early and availed of socially subsidized job skills training.

Isabelle also reported numerous volatile relationships and precarious housing situations, including being homeless for some time. Her present housing was socially provided.. A previous relationship, with someone known to her, also resulted in sexual abuse.

When asked about her premorbid personality she described herself as someone who always had difficulty regulating emotions. She reported easily becoming aggressive/agitated, anxious, and having difficulty handling stress and

disappointment. Her poor coping was also illustrated by years of nicotine, cannabis, and cocaine use, along with a history of anorexia nervosa and deliberate self-harm.

Her mental state exam demonstrated a well-groomed female, wearing heavy makeup, false nails and lashes. Her mood was mildly elated. Her manner was friendly with staff and other residents. During the interview she appeared restless often pacing around the room. Thought, affect, and cognition was appropriate. The remainder of her history and examination was unremarkable.

Discussion

It is important to firstly recognize the social determinants of health. In particular, childhood trauma can have a significant impact on one's wellbeing and research indicates a history of early trauma in 30-50% of the BD population.3

In Isabelle's case, her childhood history included neglect and physical abuse by an alcoholic biological mother. The patient also reported emotional abuse in various foster homes before she found a more permanent placement.

Research shows that maternal or paternal loss before the age of 5 also increases the risk of BD development by 4 and 2.4 times respectively.5 Not only did Isabelle not know her father, but she was also separated from her mother. Furthermore, her subsequent caregiver passed away before 5 years of age.

Animal studies have shown that early stress and poor relationships between parents and offspring contribute to poor coping and inappropriate behaviors later on in life.3 Maternal care has also been shown to influence the hypothalamic-pituitary-adrenal (HPA) axis in rats.6 The HPA axis is vital in emotion and stress regulation. Specifically, maternal care has been shown to have an influence on glucocorticoid receptor expression. A decrease in glucocorticoid receptors has been noted in humans with various psychological conditions.7 Similar epigenetic changes have also been noted to occur in people who die by suicide and have a history of child abuse; as opposed to those without such a history.7

This points to the possible etiology of the dysregulation seen in BD. Isabelle would become easily anxious about minor stressors and her mood rapidly fluctuated as well. For example, she would be very aggressive with staff and then shortly later apologize and be amiable with them.

Secondly, one needs to recognize trauma in regard to its influence on the patients' long-term outcomes. As with any illness, one's ability to cope in society will influence future outcomes and how society views that illness. It will also contribute to the overall healthcare burden regardless of the etiology of the disease.

Research indicates that early trauma, or posttraumatic stress disorder, can be a poor prognostic factor in BD management.8 It is also related to a greater severity of psychotic and depressive episodes.8 Therefore, when patients have acute exacerbations, they present with more life-threatening symptomology resulting in a greater strain on healthcare resources.

Literature also indicates that those with difficult upbringings and BD have lower overall intelligence quotient scores.9 There is also evidence that they have lower performance in attention, verbal memory, and executive functioning testing.10 These findings suggest that childhood trauma negatively influences one's cognitive capabilities and by long-term educational and career outcomes. In fact, Isabelle dropped out of school and never pursued higher education which limited her future prospects. This led to her becoming homeless at one point. Despite currently being employed she still relies on disability and aftercare to augment expenditures. Even a recent venture into further skills training was halted due to her hospitalizations.

Childhood trauma is associated with high-

er incidences of hallucinations, mania, and impulsivity in BD.12 Quicker cycling between manic and depressive episodes is noted for those with histories of physical and sexual abuse.13 This is of importance as the frequent occurrence of these symptoms inhibit recovery and daily functioning. Furthermore, rapid cycling is more difficult to treat. It also limits integration into society if one is continuously fluctuating between two extremes.

Higher levels of impulsivity associated with these BD patients is also associated with alcohol and cannabis abuse.14 This can introduce the complex implications of drug use on daily life. Not only can its use further contribute to the instability of the patient's mental health, it can impact all areas of life. Drug use effects relationships with others, finances, and forensic history. It results in further issues of addiction, dependence, and can promote poorer coping mechanisms as one might choose to mitigate stressors with recreational drugs. As BD patients already have difficulty managing stress, impulsivity, and mood, adding these drugs can have major consequences.

Additionally, patients with greater levels of trauma are also more likely to have "increased affective lability and affect intensity".11 In particular it is correlated with aggression in BD patients.15 Aggression was prominent in Isabelle's presentation which posed additional challenges to staff. Not being able to establish appropriate connections with others would also inhibit a patient's integration into society, damage relationships and affect their long-term outcomes.

Whether cognitive ability or social factors are involved, one can recognize a complex interplay of factors shaping the futures of these patients. This intricate web of factors ultimately culminates in increased hospital admissions and poorer outcomes.11 Such patients also have a worse response to maintenance medications and a higher incidence of comorbid conditions further complicating treatment. 8,10

Conclusion

It is of utmost importance for physicians to be vigilant of childhood abuse. Discussion around recognizing early trauma is vital to prompt intervention.

Consent

Verbal consent was obtained for the use of her history for educational purposes.

Conflicts of Interest

No conflicts of interest.

Acknowledgements

Special thanks to Mrs. Tanya John (psychologist) for her review and feedback for this paper.

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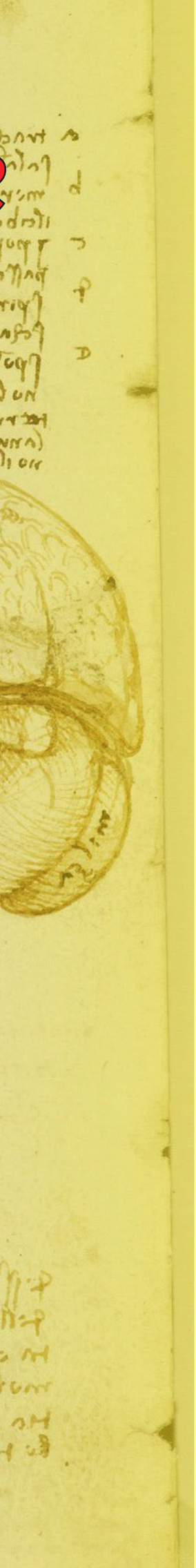
Sudden Severe Chest Pain:

An atypical presentation of an infective exacerbation of COPD

by Arlene Gutman, Nikoleta Tellios,
Reviewed by Collette Hand



Abstract

Presentation

A 59-year-old female, recent ex smoker, with a history of COPD and anxiety, presents to her GP with acute onset sharp chest pain, associated with dyspnea, diaphoresis and palpitations. On examination tachycardia, tachypnea and rhonchi were noted in the absence of fever and crepitations.

Differential Diagnosis

Her presentation raises suspicion for several conditions that require urgent treatment, including AMI, PE and pneumothorax. Few indicators of infection were present initially.

Investigations

Given the risk of life-threatening conditions included in the differential diagnosis, hospital work-up was warranted. Investigations for AMI, PE, and pneumothorax were negative. Further investigations and development of the clinical course led to the conclusion of a diagnosis of IECOPD.

Conclusion

Presentations of IECOPD can be diagnostically difficult. Although pain is not usual in IECOPD and pyrexia is common, this case illustrates the absence of such features in the presence of additional atypical features. Furthermore, acute chest pain often requires hospital investigation even if the ultimate diagnosis may be managed by the GP.

Case Background

Recent reports estimate that up to 1.5% of all general practitioner (GP) consultations are related to chest pain(1). This symptom can be distressing for patients and diagnostically challenging for GPs. While cardiovascular causes are the most common, chest pain may also present in respiratory, musculoskeletal, and gastrointestinal conditions. Given the potential serious nature of acute onset chest pain, the primary goal of management is to rule out life-threats and provide timely care. One important respiratory cause of chest pain is an infective exacerbation of chronic obstructive pulmonary disease (IECOPD). Chronic obstructive pulmonary disease (COPD) is common, with current reports estimating 180,000 individuals in Ireland(2) and 1 million individuals in the UK are diagnosed(3) with COPD. The burden of care falls on the GP, as does the responsibility of recognizing the need for further specialist care.

Case Details

A 59-year-old female with a 10-year history of COPD presented to her GP with a 3-day history of acute onset sharp, lower left-sided chest pain. The pain was slightly exacerbated by inspiration with no radiation. At onset, the patient experienced diaphoresis, palpitations, and dyspnea which continued at the GP's surgery. The patient reported she was more short of breath than normal despite increasing the use of her bronchodilators. Additional attempts to self-manage with over-the-counter analgesia and application of a heating-pad provided no relief. Notably, past medical history was significant for 2-3 IECOPD in the previous year, mixed anxiety and depression, osteoporosis, and a 13-pack/year smoking history. Relevant risk factors for an acute cardiovascular event included her age, a 13-pack/year smoking history, and longstanding respiratory disease.

On initial examination, tachycardia and tachypnea were observed along with decreased peripheral oxygen saturation, although this was within the patient's usual range. All other vitals were within normal range, including the absence of pyrexia. Mild bilateral rhonchi and normal heart sounds were heard on auscultation. Given the potential life-threatening conditions associated with acute onset chest pain, the patient was referred to hospital.

Discussions

The primary concern with acute onset chest pain is an acute myocardial infarction (AMI). In this case, the pain was associated with dyspnea, tachycardia and diaphoresis at onset, making it an important possibility to consider. Given that AMI often presents atypically in women, it cannot be excluded based on the history, although the prolonged duration of symptoms makes this diagnosis less plausible. An echocardiogram (ECG) would be the principal diagnostic tool, although ECG changes can occur on a background of chronic respiratory disease.

Acute sharp chest pain, dyspnea, and tachycardia are associated with a low diagnostic threshold for a pulmonary embolism (PE). Importantly, further investigation requires referral to emergency or hospital services. In this case, the patient was not considered high risk for a PE according to the Wells' Criteria, although patients with COPD may have their Well's score artificially lowered, since pre-existing respiratory disease provides an alternative explanation for increased dyspnea(4).

It is also important to consider conditions associated with existing comorbidities in presentations of acute chest pain. Given the history of COPD, a spontaneous pneumothorax or rib fracture caused by increased coughing are possible. Atelectasis and bullae formation in progressive COPD may contribute to a spontaneous pneumothorax, and a rib fracture must be included in the differential, especially considering the patient's history of osteoporosis. Both can be expected to present with dyspnea, decreased chest expansion, and pain

on inspiration, and both would require further imaging studies.

Furthermore, disorders of anxiety and depression commonly co-exist with COPD and can present with chest pain and dyspnea, similarly to progressive COPD or IECOPD. The symptom overlap and potential for anxiety to be triggered by COPD symptoms can make it difficult to distinguish the causative factor and may complicate the severity assessment of IECOPD. In this case the diagnosis of an acute panic attack is unlikely given the duration of the symptoms. Finally, gastrointestinal conditions such as reflux disease can be another cause of non-cardiac chest, although there were no associated gastrointestinal symptoms in this case.

Ultimately, the patient was diagnosed with IECOPD and required in-patient treatment as her symptoms evolved to include a purulent productive cough, and basal crepitations. Repeat chest X-ray and blood cultures were positive for consolidation and bacteremia, respectively. Consequently, this case raises two important points regarding the definition of IECOPD and GP evaluation of such a presentation.

IECOPD may present a diagnostic challenge especially considering the current, broad event-based definition of IECOPD in the 2019 GOLD guidelines as "an acute worsening of respiratory symptoms that result in additional therapy"(5). Recently a new symptom-based definition of IECOPD has been proposed including worsening dyspnea, which may or may not be associated with increased cough, sputum volume, or purulence (6). Ultimately, there is a need for specific clinical guidelines on identification and management of exacerbations.

This case illustrates how the symptom-based definition of IECOPD can be problematic, as the patient did not meet any of the symptom-based criteria at presentation to her GP. Such presentations pose a challenge for patient management, specifically deciding whether the patient can be adequately treated at home or whether further specialist care is required. Additionally, the use of resources and healthcare costs of referral must be balanced against the need to optimize patient outcomes and avoid treatment delays. This patient presented with sharp pleuritic chest pain, palpitations, and diaphoresis, which are concerning symptoms potentially signaling the need for urgent treatment. IECOPD mimic several conditions that must either be ruled out by the GP or acutely treated.

Finally, the National Early Warning Score (NEWS) system is used most commonly in inpatient settings for the early detection of patient deterioration. Although not its original intention, it has been suggested the calculating a pre-hospital NEWS may facilitate decision-making in regard to referrals to hospital and triage (7). By using a patient's vital signs and neurological status on their initial encounter with the GP, the GP may be able to better stratify their risk, communicate this information to emergency services and hospital teams, and contribute to improved triage of critical patients.

Conclusions

This case illustrates an atypical presentation of IECOPD, with a chief complaint of acute chest pain, which diagnostically may be confused with several conditions that require emergent treatment. In the absence of typical IECOPD features, such as pyrexia, increased cough and sputum, diagnosis in a GP setting can be particularly difficult. The use of the NEWS tool in a pre-hospital setting could be especially useful in identifying an acutely deteriorating patient in such cases. Overall, this case highlights the diagnostic difficulty and uncertainty encountered by GPs when presented with patients experiencing atypical symptoms.

Acknowledgments

We would like to thank the patient whose presentation is illustrated in this report for allowing us to share her details. Written and verbal patient consent were both obtained. We would also like to thank University College Cork (UCC), Mercy University Hospital, and the Royal College of General Practitioners (RCGP) Republic of Ireland (ROI) Faculty, for enabling us to develop this case and present it at the RCGP ROI 2019 Spring Meeting. Finally, we would like to thank Professor Colin Bradley, Department of General Practice at UCC, for his expertise and advice in the development of this report.

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Erasmus+ Exchange to Lille

by Ella Ní Chuirtín

Reviewed by
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"Is the page still damp from my tears? I'm sure we must be due to land quite soon…."

So read the opening lines from the diary I kept during my séjour in Lille, which belie the illuminating and utterly formative few months I spent there as a medical externe.

I cut a lonely figure to anyone who cared to look, anxiously poring over Google Maps and tripping over my suitcases as I emerged from my train at Gare Lille Flandres, and took my first gulp of crisp, continental air. I gazed at a swarm of nattily-clad businessmen striding towards the metro shouting at each other in rapid French, and wondered how I could possibly survive, overwhelmed and alone in this foreign city; and yet, three months later, I was asking myself how I could possibly leave it all behind.

As a third-year medical student in UCC, I was lucky enough to be afforded the opportunity to complete the clinical placements of my second semester in France, as part of the Erasmus+ programme. Given the choice between Lille and Nantes, I tentatively requested Lille because of its reputation for boasting one of the largest and most important health campuses in Northern Europe, which consistently ranks in France's top three hospitals each year.

A sprawling complex of ten hospitals, the CHU de Lille is unlike anything you could ever imagine. Instead of wards dedicated to certain specialities, entire hospitals are devoted to separate fields, allowing for the delivery of state-of-the-art, specialised, holistic patient care. As part of my 'stage,' I spent five weeks in 'Hépato-Gastro' (GI department), and four in 'Urgences' (A&E), beginning the first week of January. I remember walking in the shadow of that looming red-brick tower, 'Hôpital Huriez,' every morning and evening in the early days, feeling utterly alone in the foreign city in which I was stranded. Overwhelmed and intimidated by the white coats and unintelligible conversations around the patients' bedsides on rounds, the health system couldn't have felt more different to what I had thus far experienced on placement in Cork. 'Hôpital Huriez' was like something straight from the set of 'Grey's Anatomy;' everything was exotic, from the white coats to the eloquent politeness of doctors which is so inherent in the French language, to the passionate disputes over the care of a patient during early-morning MDT meetings.

Hierarchy and respect are paramount in French hospitals, though the structure is slightly different to the Irish system. Medical students spend six years in university, working as 'externes' for the final three years on various clinical rotations, for which they are paid. They are quite autonomous, admitting and discharging their own patients and assuming total responsibility for their hospital care. Interestingly, they must also spend a summer working in a nurse's role, which I think could be a very formative addition to our medical curriculum here. They took me on as their protégée and

Elective Experience

would check I understood the pathology relating to each patient on rounds, interpret scans and ECGs with me and take me out in the evenings to go rock climbing, which young people in Lille were crazy about!! Once qualified, they work as interns until they become 'chefs' (consultants)- there is no in-between.

I was amazed to note how relaxed the dress code seemed to be compared to Irish hospitals. The chefs were often seen in jeans and funky, scruffy runners, while nurses wore the most ostentatious earrings and dazzling hairbands. Their casual dress did not reflect their approach to patient care, however; in Gastro, every day patients successfully underwent liver transplants and in Urgences, were stitched and bandaged and referred with minimal wait times. I got to take histories and exams and present to the interns, care for my own patients, and help with ascitic taps and suturing; I remember trembling as I called the bacteriology department, my first day, to ask for a patient's lab results, desperately trying to decipher the rapid French crackling down the phone from a man who didn't realise I was newly arrived in France! I hadn't studied the language since my Leaving Cert, but total immersion is the best way to learn, and by my second placement I no longer needed to rely on my safety net, "Je comprends pas."

Lille may boast a world-renowned health campus, but the vibrant, dynamic city had much more than that to offer the medical externe released from duty. The romantic 'Vieux Lille,' the antique secluded part of the city, was my favourite haunt. Coffee and writing, with a freshly-procured pastry in a cosy French café, was my sanctuary at times when the hospital work was demanding; on moonlit walks around the 'Grand Place,' the main square, we were serenaded by a jauntily-clad jazz musician, and possibilities seemed endless. Sundays were for early-morning promenades to the market in Wazemmes, for earthy, locally-harvested fruit and vegetables. My first time, I almost ended up going hungry for the week, as I spent all the money I'd withdrawn for the market in the clothes stalls; a rookie mistake!

What I loved most about the French was their work-life balance; when asked the question, 'What do you do?' they replied with their hobbies and passions, while in Ireland, the standard answer is 'teacher,' or 'engineer.' They will emerge from a boulangerie and bite the 'quignon,' the heel of the baguette, as a ritual on their way home. The mode de vie of France is incomparable to that of any other country. I can't think of anywhere else I'd rather be.

Glossary

Séjour- sojourn

Gare Lille Flandres- the train station

CHU de Lille- the hospital campus in Lille

Hôpital Huriez- a particular hospital within the campus

Externe- a term describing 4-6th year medical students in France

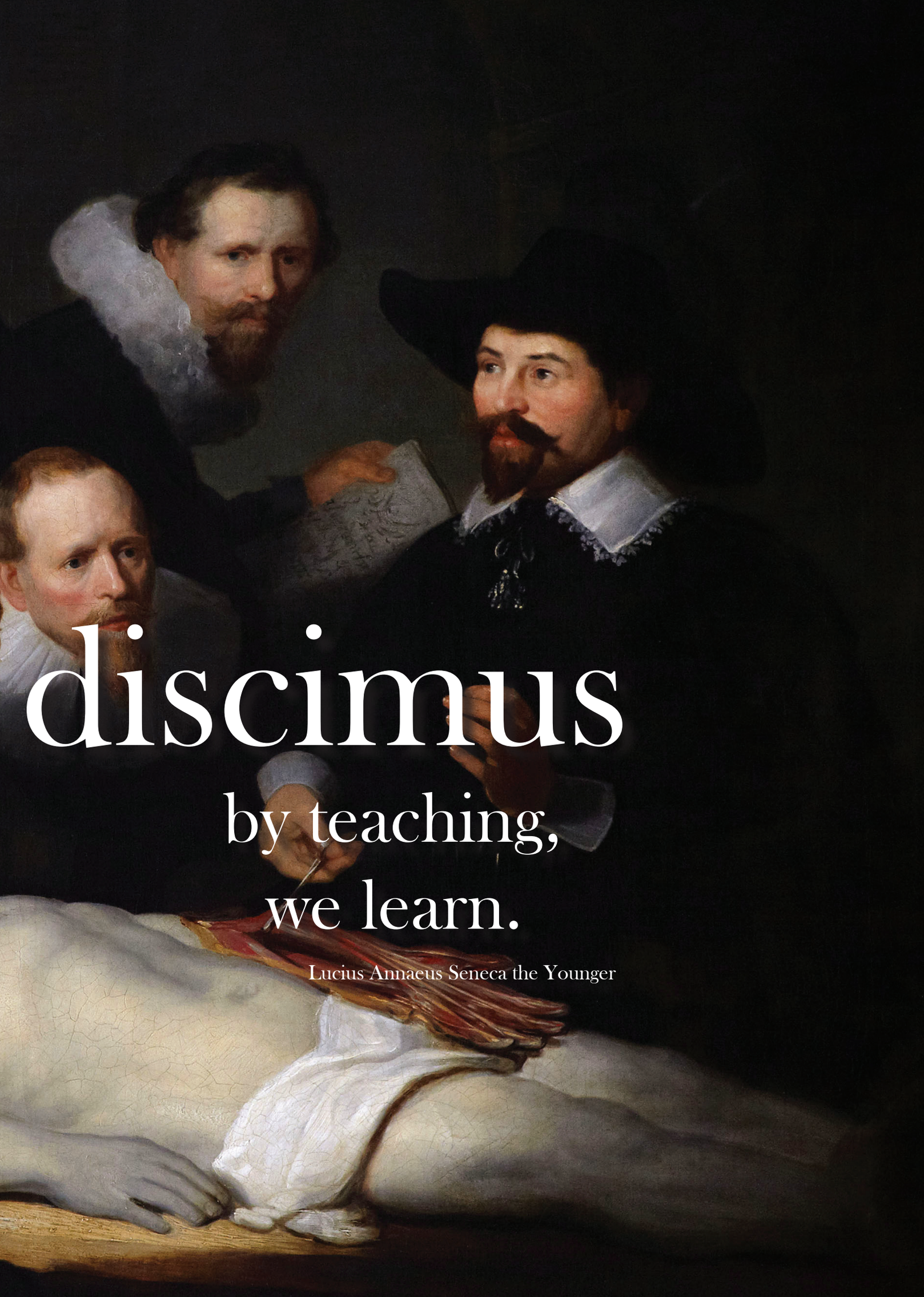
Je comprends pas- I don't understand

Vieux Lille- the old part of the city

Boulangerie- bakery

Mode de vie- way of life


“Docendo


discimus
by teaching,
we learn.
Lucius Annaeus Seneca the Younger