

# BMJ Open Misuse of medication in adult substance misuse services: a systematic review protocol

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## ABSTRACT

**Introduction** There is a growing concern about the misuse of over the counter (OTC) and prescription only medication (POM) because of the impact on physical and mental health, drug interactions, overdoses and drug-related deaths. These medicines include opioid analgesics, anxiolytics such as pregabalin and diazepam and antidepressants. This protocol outlines how a systematic review will be undertaken (during June 2021), which aims to examine the literature on the pattern of OTC and POM misuse among adults who are accessing substance misuse treatment services. It will include the types of medication being taken, prevalence and demographic characteristics of people who access treatment services.

**Methods and analysis** An electronic search will be conducted on the Cochrane, OVID Medline, Pubmed, Scopus and Web of Science databases as well as grey literature. Two independent reviewers will conduct the initial title and abstract screenings, using predetermined criteria for inclusion and exclusion. If selected for inclusion, full-text data extraction will be conducted using a pilot-tested data extraction form. A third reviewer will resolve disagreements if consensus cannot be reached. Quality and risk of bias assessment will be conducted for all included studies. A qualitative synthesis and summary of the data will be provided. If possible, a meta-analysis with heterogeneity calculation will be conducted; otherwise, Synthesis Without Meta-analysis will be undertaken for quantitative data. The reporting of this protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

**Ethics and dissemination** Ethical approval is not required. Findings will be peer reviewed, published and shared verbally, electronically and in print, with interested clinicians and policymakers.

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## INTRODUCTION

The inappropriate use (misuse) of over the counter (OTC) and prescription only medication (POM), where products are taken (and often the administration route or dose is altered), for nonmedical purposes, is a growing concern internationally.<sup>1,2</sup> Although such use of OTC and POMs does not always result in dependency, they may be used in isolation or in combination, including alongside illicit substances and/or alcohol.

## Strengths and limitations of this study

- This protocol outlines how a systematic review will be undertaken to provide a comprehensive overview of the patterns of over the counter and prescription only medication misuse by adults who are accessing substance misuse treatment services.
- Two reviewers will independently undertake study selection, data extraction and assessment of risk bias, and a third reviewer will resolve disagreements and review findings.
- The results will include the types of medication being taken, prevalence and associated characteristics, so that the needs of people who access treatment services may be better understood.
- A lack of high-quality studies may be a potential limitation.
- Where available, internationally validated tools will be used for data syntheses and assessing bias risk and quality of the findings.

Concomitant use of medicines, which have additive sedating and respiratory depressant effects, are of particular concern, especially opioids (such as fentanyl and oxycodone), benzodiazepines and gabapentinoids due to the risk of accidental overdose and drug-related deaths.<sup>3-6</sup>

OTC and POM misuse has also been associated with notable drug interactions, physical and mental health effects, such as psychosis, blood-borne virus transmission, renal failure and QT prolongation (that may result in tachycardias such as torsades de pointes), which may be life threatening.<sup>7-9</sup> Drug misuse can be associated with significant socio-economic impact for the person, their friends, family and the wider community. It may lead to incidents that may be significant, such as falls, road traffic collisions and acts of aggression or violence against self or others.<sup>10</sup>

Medication may also be taken to potentiate psychoactive effects or manage side-effects of recreational drug use, such as erectile dysfunction medication for sexual performance associated with methamphetamine.<sup>11</sup>



Motivations for OTC and POM misuse may not be solely for recreational or euphoric effect: some people may be self-medicating for withdrawal symptoms, underlying anxiety disorders or pain, as could be the case with baclofen, beta-blockers and opioids, respectively.<sup>12–14</sup> OTC and POMs may be used to change appearance such as topical steroids to change skin pigmentation<sup>15</sup> and diuretics, laxatives and stimulants for weight management.<sup>16</sup> Medicines may also be taken to improve performance, such as cognitive enhancers in academia.<sup>17</sup>

Sometimes the psychoactive effect of OTC and POMs may only become apparent when taken via an alternative route, such as Buscopan (hyoscine N-butyl bromide), which when smoked produces hallucinations, and the antitussive dextromethorphan and loperamide (for diarrhoea) when used at significantly high doses, can have euphoric effects.<sup>18–20</sup> When being misused, formulations such as buprenorphine tablets may be crushed and administered by injection,<sup>21</sup> and fentanyl may be extracted from transdermal patches and administered by all routes of administration.<sup>22</sup> Other examples include codeine, which can be combined with other substances to create new concoctions such as lean<sup>23</sup> or extracted from combination products using techniques such as ‘cold-water extraction’.<sup>24</sup>

In 2016, a report from the UK governments’ Advisory Council on the Misuse of Drugs suggested that the misuse of prescription-only painkillers, benzodiazepines, z-drugs and increasingly gabapentinoids is prevalent, with the need for increased vigilance surrounding other medicines including quetiapine, baclofen and stimulants; the need to consider OTC codeine as a ‘precursor to the misuse of prescription opioids’ was also highlighted.<sup>25</sup> Misuse may be detected and explored in a variety of ways, using qualitative methodologies such as surveys, interviews, focus groups and netnographic techniques.<sup>26–32</sup> Qualitative and quantitative information can be obtained from clinical records, surveys, prescribing data, postmarketing surveillance, pharmacovigilance studies and electronic medication dispensing systems.<sup>33–36</sup> Quantitative data may also be obtained from drug tests,<sup>37 38</sup> and as with any methodology, this has limitations; for example, OTC and POMs may not be detectable or may give false-positive results on drug tests that are routinely used in substance misuse services (SMS).<sup>20 39</sup>

While the misuse of OTC and POMs is thought to be increasing, actual prevalence remains unknown due to a lack of appropriate monitoring systems.<sup>25</sup> Public Health England (PHE) published the results of their landmark review into dependency and withdrawal associated with some POMs in 2019, which found that that prescribing rates of antidepressants and gabapentinoids among the adult English population in primary care increased in recent years to 15.8% and 3.3%, respectively; conversely, opioid analgesics, benzodiazepines and z-drugs (such as zopiclone) slightly reduced, though still prevalent with 13%, 3% and 2%, respectively, of the total population currently being prescribed these medicines.<sup>40</sup>

Consequently, the National Institute for Health and Care Excellence is developing guidelines for the management of medicines associated with dependence or withdrawal symptoms.<sup>41</sup> However, not all medicines that are used inappropriately are necessarily associated with addiction, dependency or withdrawal symptoms, and the PHE review<sup>40</sup> did not consider all types of medication or different treatment settings such as specialist SMS.

The UK’s Clinical Guidelines on Drug Misuse and Dependence<sup>42</sup> outline that there is a limited evidence base available to inform the clinical management of individuals who require support. This is especially important where illicit substances are used alongside OTC and/or POMs because this may be associated with a lower quality of life and greater mental health issues.<sup>43</sup> It is, therefore, essential to be able to offer timely and effective interventions to reduce the risk of using other substances, experiencing more severe functional problems and riskier drug-related behaviours.<sup>44</sup> Additionally, substitute treatment used in SMS may also be used inappropriately and people who access SMS are more likely to experience comorbid mental health conditions, be prescribed psychotropic medication and for unlicensed indications.<sup>45 46</sup>

Data from the USA suggest that once people who need support with their problematic OTC and/or POM use are engaged in treatment, then retention and abstinence rates are thought to be favourable, so identifying their demographic characteristics may assist with improving associated SMS outcomes.<sup>47 48</sup> The characteristics of people who use OTC and/or POMs may be different in other countries such as the UK and may be different to those who choose to primarily use ‘street’ drugs; however, people who use ‘street’ drugs or who may be in receipt of substitute treatments from SMS are also known to misuse OTC and POMs.<sup>49 50</sup> For example, in the UK, 69% of people seeking support from SMS are men<sup>51</sup>; however, the 2019 PHE review and the associated publication by Marsden *et al*<sup>52</sup> identified higher rates of prescribing for women of medication associated with dependency and withdrawal.<sup>40</sup> Other studies have found that women may have a greater propensity for some types of OTC and POM misuse or be more likely to experience more severe outcomes and subsequently account for an increasing proportion of associated emergency department admissions.<sup>53–55</sup> Furthermore, older age, residing in areas of greater deprivation, comorbid chronic pain issues and HIV-positive status may also increase risk of misuse, but this may vary by the type of medication.<sup>40 47 53–59</sup> Such medicines may be legally sourced via prescriptions and pharmacy sales and sometimes multiple outlets or healthcare professionals are visited to obtain supplies; however, they may also be obtained illegally, for example, from street dealers or unregulated internet purchases.<sup>49</sup>

There are currently no other known systematic reviews that have focused on the misuse of OTC or POM by people accessing SMS. This protocol is for such a systematic review to be undertaken, in line with Preferred Reporting Items

for Systematic Reviews and Meta-Analyses (PRISMA),<sup>60</sup> and using the PRISMA-Protocols (PRISMA-P) checklist.<sup>61</sup>

### Aim and objectives

This protocol outlines how a systematic review will be undertaken, which aims to examine the literature on the pattern of OTC and POM misuse among adults who are accessing substance misuse treatment services. The objectives of the systematic review are to identify the types of medication being taken, the prevalence of use and associated demographic characteristics.

## METHODS

### Eligibility criteria

This review will consist of published studies that must meet all the following criteria:

- ▶ Adult participants (18 years or over).
- ▶ Individuals receiving interventions for substance misuse in any setting (eg, prison, community, hospital).
- ▶ People who are inappropriately using (misusing) OTC and/or POM for nonmedical purposes.
- ▶ Individuals in receipt of psychological and/or pharmacological interventions for their substance use.

Prescription medication will not include those that are being prescribed to the individual for the management of their substance misuse disorder. There will be no other restrictions on the type of study population or publication time period. Letters and comments outlining the views, experiences and opinions of individual professionals, researchers, commentators or patients will be excluded; however, reports that summarise and/or collate individual experiences will be considered. For practical reasons, results from all countries and in all languages will be noted; however, only English language results will be considered.

### Information sources

Library staff from Aston University verified the suitability of the search strategy. The reference lists of eligible studies will be manually searched to identify any additional relevant citations to ensure a comprehensive search.

### Search

A comprehensive search of the published literature will be undertaken during June 2021 using the Cochrane,<sup>62</sup> OVID Medline,<sup>63</sup> Pubmed,<sup>64</sup> Scopus<sup>65</sup> and Web of Science Core Collection<sup>66</sup> databases. Grey literature will also be checked for relevant information. A combination of keywords, medical subject heading and Boolean operator terms related to prescription, and OTC medication misuse in substance misuse treatment will be used such as (Over-the-Counter Drug Misuse) OR (Prescription Drug Misuse) AND (Substance Abuse Treatment Centers). See online supplemental file 1.

### Study selection

Two independent reviewers (RG and LM) will conduct the initial title and abstract screenings, followed by full-text

reviews, using predetermined criteria for inclusion and exclusion. A third reviewer (IM) will resolve disagreements if consensus cannot be reached.

### Data collection process

If selected for inclusion, full-text data extraction will be conducted using a pilot-tested data extraction form. An iterative approach will be taken to improve the usability and to assure the functionality of the forms during the piloting process. Completed pilot forms will be assessed to ensure that they are fit for purpose and that a consistent approach is taken by both reviewers. Where possible, the authors of the papers will be contacted to provide any missing information. The extracted data will be simultaneously captured by both reviewers using Google forms, which all reviewers are familiar with. Patients were not directly involved in the protocol design study and participant recruitment is not required for a systematic review, so disseminating findings to participants is not applicable.

### Data items

The form prompts for retrieval of data including primary author surname, year of publication, title of the publication and journal name, details of medication and other substances, sample size and characteristics, study design, setting, methodology, statistical methods and results, summary of findings and limitations.

### Risk of bias

Quality scores from the Mixed Methods Appraisal Tool (MMAT)<sup>67</sup> will be used to assess the risk of bias as this tool accommodates quantitative, qualitative and mixed methods, so the same tool can be used for all studies. If appropriate, for systematic reviews, the MMAT will be supplemented by A Measurement Tool to Assess Systematic Reviews version 2.<sup>68</sup> They will be applied by the reviewers (RG and LM) independently, and the results will be tabulated to enable easy comparison. Similarly, as with data extraction methodology, discrepancies will be discussed and a third reviewer (IM) will be consulted to resolve any disagreements.

### Summary measures

OTC and POM misuse by adults who are receiving treatment for substance misuse may be determined in a multitude of ways. The identification of the types of medication being taken, prevalence and associated demographic characteristics will be considered.

### Patient and public involvement

No patient involved.

### Synthesis of results

All included studies will be appraised with a qualitative summary. The synthesis of qualitative data will follow a thematic analysis approach and the main review findings will be summarised in table format using MS Excel. If the quantitative data allow, a meta-analysis will be undertaken and the outcomes captured in a forest plot. Otherwise,



numerical descriptors will be captured as a narrative. Quantitative data synthesis methodology and potential for meta-analysis will be dependent on the number and quality of studies identified. Heterogeneity will be assessed using the  $I^2$  test, and as outlined by Higgins and Green,<sup>69</sup> heterogeneity is impacted by a variety of factors, so cut-off values will not be enforced; however, heterogeneity will be considered likely if  $I^2$  is greater than 40%. If this occurs, subgroup analyses will be undertaken and it may be more likely to occur, for example, for age, gender and type of medication.

As proposed by Campbell *et al*<sup>70</sup>, if a meta-analysis is not possible, then Synthesis Without Meta-analysis (SWiM) will be undertaken due to the shortcomings associated with narrative synthesis, and in order to complement PRISMA. Similar to the data extraction process, an independent second review reviewer (LM) will quality assure the analysis, and discrepancies between reviewers will be identified and resolved through discussion (with a third reviewer (IM) where necessary). The resulting cumulative strength of the quality of evidence will be assessed using Grading of Recommendations, Assessment, Development and Evaluation.<sup>71</sup>

### Ethics and dissemination

Ethical approval is not required for a secondary data analysis. The findings will be published in a peer-reviewed journal and at conferences, shared verbally, electronically and in print, with interested clinicians and policymakers.

### DISCUSSION

As all reviewers will be using the same data collection form, which is piloted for suitability of use, this will enable the data extraction process to be standardised. Having two reviewers independently undertaking study selection, data extraction and assessment of risk bias and a third reviewer to resolve disagreements and review findings as well as the use of the MMAT<sup>67</sup> will strengthen the quality assurance process.

Internationally validated tools will be used for data syntheses where available. For example, the findings will be reported in line with PRISMA,<sup>60</sup> and a flow diagram will be used to capture the study selection (and exclusion) process. A lack of high-quality studies may be a limitation, and their diversity may further limit the potential for meta-analyses for quantitative data. If this is the case, then SWiM<sup>70</sup> will be used to add robustness.

Undertaking this systematic review will enable a greater understanding of the current published evidence base relating to the pattern of OTC and POM misuse by adults who are accessing SMS. The resulting critique of the findings is important given the increasing concerns about this issue and will be useful to identify areas on which to focus future research.

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**Author note** LM became involved in this work prior to commencing employment at Gilead Sciences, who have no input or involvement in this work.

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