

Developing a classification of trials based pharmacological interventions for schizophrenia

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Keywords:	Classification, Randomised controlled trial (RCT), Review, systematic, Database Management, Information storage and retrieval, Mental health
Abstract:	<p>Background: Systematic reviewing is a time-consuming and resource-intensive process. Information Specialists are maintaining study-based registers to facilitate efficient conduct of systematic reviews. Classification of study-level meta-data -such as interventions -can result in much more accurate searches, saving time in the early steps of systematic reviewing.</p> <p>Objective: To classify all pharmacological interventions from all schizophrenia trials.</p> <p>Methods: We used Cochrane Schizophrenia's Study-Based Register as the source of trials, Emtree and MeSH for synonyms, AdisInsight and CT.gov for research drugs, and WHO ATC for marketed drugs.</p> <p>Results: One third of tested interventions on patients with schizophrenia are pharmacological (816; belonging to 106 clinical classes) with antipsychotic drugs being the most researched (15.1%). Only 528 of these medications are listed in WHO ATC. Around one third of these drug interventions are seen only in research (236; from 21 pharmacological/biochemical classes). Within the pharmacological interventions we identified 28 'qualifiers' including dose, route, and timing of drug delivery.</p> <p>Conclusion: Identification and classification of pharmacological interventions from trials requires use of many sources of information none of which are inclusive of all drugs. Limitations of each source is helpful to understand. Classification of non-pharmacological interventions is now a priority for clinical and information scientists and professionals.</p>

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Developing a classification of trials based pharmacological interventions for schizophrenia

True ignorance is not the absence of knowledge, but the refusal to acquire it.

Karl Popper

I have neither the ability, knowledge, time, or space to classify all present-day therapies. All I feel capable of is a rough classification ...

Archie Cochrane

Abstract

Background: Systematic reviewing is a time-consuming and resource-intensive process. Information Specialists are maintaining study-based registers to facilitate efficient conduct of systematic reviews. Classification of study-level meta-data -such as interventions –can result in much more accurate searches, saving time in the early steps of systematic reviewing.

Objective: To classify all pharmacological interventions from all schizophrenia trials.

Methods: We used Cochrane Schizophrenia’s Study-Based Register as the source of trials, Emtree and MeSH for synonyms, AdisInsight and CT.gov for research drugs, and WHO ATC for marketed drugs.

Results: One third of tested interventions on patients with schizophrenia are pharmacological (816; belonging to 106 clinical classes) with antipsychotic drugs being the most researched (15.1%). Only 528 of these medications are listed in WHO ATC. Around one third of these drug interventions are seen only in research (236; from 21 pharmacological/biochemical classes). Within the pharmacological interventions we identified 28 ‘qualifiers’ including dose, route, and timing of drug delivery.

Conclusion: Identification and classification of pharmacological interventions from trials requires use of many sources of information none of which are inclusive of all drugs. Limitations of each source is helpful to understand. Classification of non-pharmacological interventions is now a priority for clinical and information scientists and professionals.

Keywords

Classification; data management; information storage and retrieval; mental health; Randomised Controlled Trial (RCT); review, systematic

Key Messages for Practice

- There is no comprehensive resource to index/classify pharmacological interventions. Consider using a combination of resources to identify drug terms and drug classifications.
- WHO ATC has gaps for new drugs and regional pharmacological interventions from non-English speaking world - specifically drugs discovered/used in Japan.
- Practice of searching based on the *known* drug names and synonyms may not retrieve all the relevant studies - but only most relevant studies from the English-speaking world.

Background

To test the effects of new drugs, researchers often use the randomised controlled trial (RCT) study design. In these studies, participants are randomly assigned to different treatment groups. After a period of follow-up, outcomes are compared (Clarke et al., 2019). Related studies are often repeated to increase the certainty and applicability of findings. All relevant evidence from trials helps inform policy and clinical decisions and systematic reviews of the RCTs help this happen. To *conduct* a systematic review researchers follow a process that may include some or all these steps (Higgins & Green, 2011):

1. Searching all relevant databases;
2. Screening the title and abstract of search results for review eligibility;
3. Obtaining full reports of potentially eligible search results;
4. Screening full reports to identify the included studies;
5. Concatenating multiple reports of the same study to avoid multiple counting;
6. Extracting quantitative and qualitative data from included studies;
7. Analysing data; and
8. Writing the final report.

Information Specialists' involvement in systematic reviewing improves the quality of searches (Koffel & Rethlefsen, 2016; Meert, Torabi, & Costella, 2016). During the past 25 years – with the development of specialised registers in the Cochrane Collaboration – the role of some of the Information Specialists has developed beyond searching to involve screening and the development of subject-specific reference-based bibliographic registers of RCTs (Metzendorf & Featherstone, 2018). Furthermore, emergence of study-based registers, a sub-type of specialised registers, extended the Information Specialists' role to include data science expertise (Shokraneh & Adams, 2019). In study-based registers, all references or reports of the same study are linked to their study record – the meta-record (Shokraneh & Adams, 2017). This meta-record contains data about the study e.g. health care condition, interventions, outcomes (so called PICO) (Shokraneh, 2016). It is then possible to search *study* fields such as interventions in addition to reference fields (e.g. title, abstract, etc.). If the reference-based registers

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3 were like a stack of books in one subject area with no classification, a study-based database could be
4 compared to an organised library with a classification system based on PICO (Shokraneh & Adams,
5 2019). For this level of organisation to be useful, however, PICO meta-data has to be extracted from the
6 full text reports of each study using existing or new controlled vocabularies (**Figure 1**).
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9 **Figure 1: Study-Based Register versus Reference-Based Register**
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13 While Medical Subject Headings (MeSH), Excerpta Medica Tree (Emtree), and other controlled
14 vocabularies are used to assist information retrieval, a rigorous classification based on the PICO meta-
15 data has not yet been published. This paper addresses this deficit for pharmacological interventions ('I'
16 in PICO) relevant to people with schizophrenia. Such classification can improve the performance of an
17 any information retrieval system and increase the relevancy of search results (Ingwersen & Järvelin,
18 2005) that may result in the need for minimum effort in screening search results. Using a classification
19 system to code studies with their PICO elements means that, the Information Specialist can complete
20 the first five steps outlined above before they are given to the reviewers, saving time in the overall
21 process (waste-reduction) (Shokraneh & Adams, 2019).
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25 Objective

26 To develop and share learned lessons, and to make public the classification of pharmacological
27 interventions from the comprehensive study-based register of schizophrenia RCTs.
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30 Audience

31 Those who deal with classification of interventions in any context. We, however, followed the
32 recommendation by knowledge organisation theoreticians to keep the classification within its context
33 (G. C. Bowker & Star, 1999) and intentionally remind the reader that this classification was born out of
34 systematic reviews and a specialised trials register and wider generalisation would need to be tested.
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37 We have used the terms drug, medication, and pharmacological intervention interchangeably and as
38 synonyms.
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42 Methods

43 Source of data: Cochrane Schizophrenia Group's Study-Based Register of Trials

44 This database was started nearly 30 years ago (Adams & Gelder, 1994) to facilitate the systematic
45 review process in the Cochrane Schizophrenia Group. Currently, it supports running the searches for
46 over 324 maintained Cochrane reviews (increasing at rate of 25-30/year). This database is being
47 maintained using the MeerKat 1.6 computer program and details of this register are described
48 elsewhere (Cochrane Schizophrenia Group, 2019; F. Shokraneh & C.E. Adams, 2020).
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Timeline and resource

This research took place between 17 December 2014 and 6 January 2019 by a full-time Information Specialist.

Piloting

In December 2014, the database already contained 9200 intervention labels for the approximately 18,500 trials. It seemed unlikely that a new intervention was tested in every second study. Investigating only interventions starting with the letter 'A' showed that over half were duplicates undetected by the software because of:

- (Human) errors in spelling;
- Differences between American and British spelling;
- Unique entry of synonyms/brand names rather than use of generic name;
- Indexing aspects of *administration* or *actions* rather than the drug itself.

Despite the attempted development of a standard protocol for indexing PICO meta-data in April 2004 as part of the PsiTri project (EU-PSI Coding Manual Working Group, 2004) there was clearly a problem in consistency. This may have happened because of changes in geography or human resources or infrastructures that the organisation loses knowledge or a process (G. C. Bowker, 1997) usually unintentionally – so-called organizational forgetting (de Holan, Phillips, & Lawrence, 2014).

Data cleaning

To solve these problems, FS corrected spelling errors, separated the interventions from intervention qualifiers (subheadings) and made sure a single preferred controlled term was employed instead of multiple synonyms of the same drug. The project then required development of a classification system in order to facilitate the process of systematic reviewing.

Current subjective classification in titles of Cochrane reviews

FS initially relied on the author-led classification within Cochrane Schizophrenia's existing systematic reviews. These 324 reviews, although the largest sample of maintained systematic reviews in existence, still cover only a subset of pharmaceutical approaches tested in all schizophrenia trials. Currently, classification from titles would generate many omissions. In addition, even within these titles, there are inconsistencies and synonyms. Clearly, a classification system was needed.

Choice of objective tools

FS investigated AdisInsight, Emtree, MeSH, British National Formulary (BNF), and WHO Anatomical Therapeutic Chemical classification system (WHO ATC) for their indexing of drugs starting with the letter 'A'.

- AdisInsight - the most comprehensive source for recent research drugs (sourcing part of its data from ClinicalTrials.Gov);
- BNF - suggested practical *clinical* classes for some drugs but coverage was very limited.

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- 4 - Emtree and MeSH - solely useful in identifying different synonyms of old research drugs because
- 5 of their longevity - not good at identifying drugs used outside Western Europe and the English
- 6 speaking world;
- 7 - WHO ATC - the best available classification option for approved, marketed drugs;
- 8

9 None of these tools covered all 'A' drug interventions in the register of trials. Because it is a priority for
10 Cochrane reviews to support clinical practice, the decision was taken to use WHO ATC. FS indexed every
11 compound with the generic drug name, assigned WHO ATC code, the clinical class and pharmacological
12 action class or chemical structure/group class. Where the intervention in the RCT referred to more than
13 one drug (i.e. a class of drugs), FS used an asterisk after the term to indicate this (see Online Appendix).

14 Sources of synonyms and identifying non-marketed drug names

15 During a drug's life cycle, a drug may have a chemical name, research names, a generic name and brand
16 names. These names also reflect different phases of drug development (Scutti, 2016). Although WHO
17 ATC is the most comprehensive source of classification of marketed drugs, it does not support searches
18 for synonyms. FS, therefore, used Emtree (inclusive of MeSH terms) for this and, in all cases, recorded
19 the generic name. Thereafter FS used WHO ATC to find the drug's class name, tree and number.

20 For drugs not in the WHO ATC:

- 21 1. AdisInsight was used to cover recent drugs in RCTs; then
- 22 2. ClinicalTrials.Gov searched to cover recent drugs not in AdisInsight; then
- 23 3. Google searched (inclusive of Google Books) to cover old drugs; and finally
- 24 4. Classes suggested/claimed within the RCT reports used to cover drugs unclassified in other
25 sources.

26 For a *marketed* drug not within WHO ATC, the same data as for marketed drugs were recorded, with the
27 nearest possible WHO ATC code and the uncertainty in last digits and letter was expressed by use of
28 question marks '?' to indicate unknown digits and letters that are pending and to be assigned by WHO
29 ATC.

30 Drugs not on the market and their development status

31 We considered a drug to be a 'drug only used in research' if it met the following criteria:

- 32 • Not listed in WHO ATC; and
- 33 • Despite searching current major relevant resources, no wider/generic reference to the drug was
34 identified.

35 During the indexing process, FS recorded the last used name of the drug, development status, potential
36 clinical class, and potential pharmacological action or chemical structure/group (**Table 1**).

Please insert Table 1

Double-checking

During cleaning of data it became clear that some interventions were missing from the original Cochrane Schizophrenia Group's Register's study records. Human errors are inevitable in a task of this size but these errors make searches unreliable. FS double-checked all indexing and, in the case of discrepancy or complexity, consulted a specialist psychiatrist.

Indexing principles

We indexed what interventions patients had been *randomised to*- although this was not always straightforward. For example, sometimes participants were randomised to a combination of drugs or two different doses of the same drug. In these cases we applied qualifiers as we had learnt was necessary from our pilot study above. We also tried to follow the indexing principles:

- *Literary Warranty* (Rodriguez, 2008): the drug enters the classification system if it has been used in one of the treatment arms (or as part of the randomised treatment) in one or more RCTs.
- *Co-ordination* (Bachrach & Charen, 1978): when impossible to describe an intervention using a single index term more than one concept or qualifiers were used to describe the intervention.
- *Multiplicity* (Bachrach & Charen, 1978): indexing covered all interventions in the randomised arms- even if the drug was not specific or was not a major part of the treatment.
- *Specificity* (Bachrach & Charen, 1978): indexing focused on the most specific intervention rather than broad classes.

In rare cases pragmatic decisions had to be made. For example, where researchers have randomised people to a *class* of drugs—without naming the specific compounds—drug-level indexing was impossible.

Theoretical context for current classification

As a result of using WHO ATC, which is updated centrally and is stable, the classification scheme partly followed the Practicalist approach to knowledge organization (Hjørland, 2016b). However, the classification used by the *systematic reviewers* for Cochrane reviews follows a expert-agreed consensus-based approach (Hjørland, 2016b). Also, we utilized a facet-analytic approach as the intervention classification also involved drug 'facets' – such as route of administration, dosage, and, in some cases, flavour or colour. Many trials use a combination of interventions and some compare an aspect or facet of one intervention (i.e. oral form versus injection of the same drug). This approach has the advantage of being the 'most explicit' and a 'pure theoretical approach' (Hjørland, 2016a) but we also found it practical when it came to classification of facets in trial comparisons.

Results

Existing classification within the systematic reviews

After nearly 30 years of working, still only 10% of RCTs have been included in systematic reviews produced by the Cochrane Schizophrenia Group – but, limited though this is, these trials are likely to

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3 represent a subset of comparisons that are considered important by clinicians, policy makers,
4 researchers and consumers of care. This was the starting point for the classification of pharmacological
5 interventions (summarised in **Table 2**) and identified 19 classes of drugs. Thirteen classes, however,
6 were based on pharmacological action of drugs, three on clinical action and the last three based on
7 chemical group/structure.
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10 **Please insert Table 2**

13 One third of tested schizophrenia treatments are drugs

14 After cleaning 9,200 interventions, 2,792 remained unique. About one third (816) are pharmacological
15 interventions 71% of which are on the market (**Table 3**).
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19 **Please insert Table 3**

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23 Most of these pharmacological interventions (65%) have been classified in WHO ATC (528 drugs).
24 However, an additional 52 drugs were not present in WHO ATC but are in the market (**Table 4**). Most of
25 these 52 are used as chemical food additives; however, some were country-specific drugs such as
26 Blonanserin, Spiperone, Perospirone, and Timiperone (Japan).
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31 **Please insert Table 4**

35 WHO ATC classes

36 There are 13 major anatomical categories in WHO ATC and, predictably, most of the drugs in the
37 Cochrane Schizophrenia Register belong to the 'Nervous System Drugs' (49.3 %). At the finer 'clinical
38 class' level, these drugs belong to 106 classes – with the antipsychotics being the most researched
39 (15.1%). WHO ATC also provides a 'pharmacological action and/or chemical structure' class (**Table 5**).
40 Drugs may affect more than one receptor and have more than one pharmacological action. FS grouped
41 the major pharmacological mechanism of action of research drugs into 21 major categories of either
42 pharmacological action or biochemical group. Over 40% of research drugs target one or more of
43 Serotonin, Dopamine, Acetylcholine, and GABA A receptors.
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48 Considerations when using the WHO ATC

49 False 'classes' such as atypical/typical or first/second generations antipsychotics were not listed in WHO
50 ATC - unlike the International Classification of Diseases (ICD) where the industry – insurance companies,
51 industrial firms, and pharmaceutical companies – had an influence on the classification (G. Bowker &
52 Star, 1991).
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3 Although WHO ATC is currently the best available classification for our purpose, it does have important
4 known limitations (Merabti et al., 2011) and we added with the following:
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- 6 • Duplicates: WHO ATC contains many duplicates. This is not only where a drug is classed -
7 justifiably - in two places but genuine duplication of the same drug appearing in the search
8 results more than once with the same class code.
 - 9 • No ordered hierarchy: For example, after the overarching anatomical class, the next class down
10 is sometimes clinical, sometimes pharmacological and sometimes a chemical structure or group.
 - 11 • Listed drugs limited by assignment to anatomical class: For example, a drug listed under
12 'ophthalmologicals' is being used by people with schizophrenia not because of this anatomical
13 class but because of its pharmacological (anticholinergic) action. As a result, the anatomical
14 classification will appear odd for those using the classification for condition-specific indexing.
 - 15 • Synonyms: It is not possible to search synonyms of drugs.
 - 16 • Spelling: WHO ATC relies on a European spelling of the generic drug name (i.e. amfetamine not
17 amphetamine) and there is no function to recognise potential differences in spelling when
18 searching.
 - 19 • Different binders of the same drug not covered: For example, the important distinction between
20 Zuclopenthixol *acetate* and Zuclopenthixol *decanoate* is not made.
 - 21 • Marketed drugs: WHO ATC largely – but not entirely comprehensively (see below) – relies on
22 drugs already at market. It does not list experimental or upcoming drugs or classes.
 - 23 • Geographical bias: it is largely based on drugs from Western countries.
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33 **Please insert Table 5**

34 35 36 37 **Qualifiers (subheadings)**

38 The most frequently used 'qualifiers' from the perspective of systematic reviews were used to develop
39 the main set employed in the final classification (**Table 6**).
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44 **Please insert Table 6**

45 46 47 **One third of tested schizophrenia drugs are not on the market**

48 The development status of 236 of pharmacological interventions were 'developing', or in 'unclear
49 development state' or 'stopped' (29% of reported schizophrenia drugs in RCTs). The majority of research
50 drugs were targeting nervous system and were purported antipsychotics, anti-Parkinson agents, and
51 antidepressants. The clinical purpose of 65 of these drugs (27.5%) is not available.
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54 As available in the **Online Appendix**, only 19 of these drugs (8%) were withdrawn post-marketing
55 (Methitural, Phencyclidine, Benzquinamide, Flurothyl, Lysergic Acid Diethylamide (LSD), Picrotoxin,
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3 Benactyzine, Etryptamine, Pheniprazine, Azacyclonol, Carphenazine, Mepazine, and Piperacetazine). The
4 rest either are still being researched, stopped, or are in unclear development state.
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8 The new learned lessons

9 We already discussed the benefits of a study-based register for preventing errors in systematic
10 reviewing (Shokraneh & Adams, 2019; Shokraneh & Adams, 2017). However, this study has uncovered
11 two additional errors that could be prevented because of the use of a study-based register with a
12 classification system:
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- 14 • *Out-of-date status of studies*: it is easy for systematic reviewers to misclassify the status of the
15 study as 'ongoing' - where details are incomplete and not enough to include or exclude a study
16 in a review - without the full availability of all reports of a study. Through standardisation of the
17 interventions we merged many what we had previously thought of as separate studies into one
18 study. As a result, status of some studies changed from 'ongoing' to 'completed'. The better
19 indexing resulted in more accurate concatenation and complete study records so that a more
20 informed decision could be made about how to use the study data within the review.
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- 22 • *Exclusion because of unknown intervention names*: systematic review authors search for all drug
23 names *known* to them. They (and Information Specialists working with them) are unaware of
24 the *unknown* names of the same drug. Clearly, there are names for even very widely used
25 compounds that are unfamiliar to many. Use of generic names for indexing, at the study level,
26 helps avoid failing to identify studies which originate from places using very unfamiliar drug
27 names. For example, 'ditan' is one brand name for 'diazepam' *and* several other drugs (!). It is
28 not mentioned in MeSH or Emtree as entry term under any drug. It is also the name of a
29 traditional Chinese medicine. To further confuse matters, 'ditans' refers to a class of drugs in the
30 'Western' medicine. After detailed investigation we identified that the intervention 'ditan' was a
31 brand name for 'diazepam' employed in far East. The 'ditan' RCT which had been missing from
32 assessment in the published review on benzodiazepines (Dold et al., 2012) was then identified
33 and added to the ongoing update of the review.
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43 Discussion

44 This research is the first effort to classify pharmacological interventions tested within a defined group of
45 RCTs. The source of RCTs – the Study-Based Register of the Cochrane Schizophrenia Group – has
46 coverage from 1949 (the date of the very first relevant RCT (Kitzinger, Arnold, & et al., 1949)) to the
47 present and contains any published or unpublished document regardless of type or language. Accessing
48 this comprehensive database affords opportunity to categorise all drugs tested in one important corner
49 of health care. Information Specialists with intimate knowledge of a certain medical speciality can
50 classify the relevant interventions and have the best chance in keeping abreast of the changing names of
51 drugs. Having said this, this study found important trials that had been buried in the register for over
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3 two decades that had not been included in relevant reviews because the brand name of the drug was
4 unknown in Western medicine.
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6 The number of drugs tested for people with schizophrenia was impressive. Certainly, the heterogeneous
7 pharmacogenetic profile of patients, the different states and stages of psychosis (Lieberman & First,
8 2018), the varying symptom profiles of schizophrenia (Steeds, Carhart-Harris, & Stone, 2015), and co-
9 morbidities (iatrogenic and otherwise) all have added to the need for a long list of medications used for
10 treating schizophrenia. However, probably the greatest driver for developing and testing alternative
11 drugs is that, although the drugs are effective, they are far from perfect. For example, although
12 effective, antipsychotics are widely disliked due to their side effects and because they unpleasant to
13 take/administer. They may be only partially effective leaving the person experiencing new adverse
14 effects along with old half-responsive psychotic symptoms. The number of drugs may reflect not only
15 the complexity of the illness or illnesses, but also the vigour of the search for a better treatment for this
16 most difficult of conditions.
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21 We concur that classifications should be used in their own context (G. Bowker, 1998). We identified
22 many medications in WHO ATC with anatomical classes *irrelevant* to schizophrenia yet the
23 pharmacological action was relevant. Our classification system was developed to be used in the context
24 of interventions from trials of people with schizophrenia. Any use for other purposes may require
25 modifications. The materials used as the source of interventions were the RCTs reported by medical
26 researchers and the classification systems used to standardize the collected interventions – just like
27 other medical classification systems – were not necessarily designed based on clinicians' or systematic
28 reviewers' needs (G. Bowker & Star, 1991). For example, WHO ATC classifies 'Lithium' as an
29 antipsychotic drug but no systematic review of antipsychotic drugs includes 'Lithium'. Reviewers
30 consistently refer to lithium as a 'Mood Stabilizer' - a class of drugs that has no place in WHO ATC. In
31 some cases, to meet both WHO ATC class and reviewers' need, we kept both classes working in parallel.
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36 [Are systematic reviewers also good classification developers?](#)

37 Although the Cochrane review titles – developed following PICO framework – were a good starting point
38 for identifying important classes of interventions, it is clear that the systematic reviewers have not
39 followed a standard classification system when choosing terminology for review titles. Some titles are
40 based on clinical class, others on pharmacological class, and, in some cases, there were duplicate terms
41 for describing the same concept (i.e. typical antipsychotics and first generation antipsychotics); the
42 latter concept being not a true class of drug but more one imposed by industry with pecuniary interests.
43 It is not clear that the titling of Cochrane reviews has to be this inconsistent. It is important to
44 communicate clearly the target of the review in terms that make the work easy to identify and access. In
45 this, classification can help. It may be that, in general, the title of the Cochrane review should use
46 generic drug names or pharmacological classes as default. Titling of a Cochrane Overview (a review of
47 reviews), however, may be best to favour either pharmacological classes or/and clinical class.
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53 [What qualifies as qualifier?](#)

54 Until now, no classification system has considered useful qualifiers of pharmacological interventions. We
55 had to develop the list of qualifiers for both existing reviews and, looking to the future, as yet un-
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3 reviewed RCTs. We considered a concept/aspect as a 'qualifier' when people were randomised to an
4 'aspect' or facet of the same drug – for example timing of when the same drug is given, or generic vs.
5 trade forms of the same compound. Before the end of this classification effort, there was little
6 information on what aspects of the drugs have been targeted and tested in RCTs. Now we are aware
7 that many have been tested - from the size and flavour of pill to the depth of injection – and that these
8 qualifiers can also be the focus new systematic reviews.
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11 **Marketed non-WHO ATC drugs**

12 There are marketed schizophrenia drugs in China, Czech Republic and Japan that are not listed in WHO
13 ATC. These omissions may reflect some degree of a language barrier to entry on WHO ATC. A highly
14 specific indexing project such as this one is able to identify such omissions but is also vulnerable to
15 them. For example, Japan's ICHUSHI – historically, the second medical bibliographic database after
16 MEDLINE and having 12 million records – is currently inaccessible to Cochrane Schizophrenia Group and
17 may contain more trials of other drugs unknown to us. With illnesses such as schizophrenia, for which
18 care must be tailored depending on many variables including individual response – however
19 idiosyncratic – every potential drug treatment is an important addition to the armoury.
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24 **One third of schizophrenia drugs are not on the market**

25 Overall, there was poor reporting of the reasons why drugs had not reached the market. Where
26 AdisInsight reported that a drug had ceased being tested, it gave no reason. It may be that these drugs
27 were ineffective or toxic. This should be reported to prevent more trials. Other drugs may have been
28 effective but not been brought to market for reasons of finance, business strategy (Bannister, Adams, &
29 Shokraneh, 2019), or organisational forgetting during the merger of pharmaceutical companies. This
30 also should be made clear for as the chemical is off-patent it could be made available again as another
31 treatment for this difficult illness.
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35 **Receptors targeted by non-marketed drugs**

36 There could be benefits to study retrieval if receptor blockage profiles were classified alongside drugs.
37 The dopamine (D) hypothesis, accepted among many schizophrenia researchers, explains that
38 hypostimulation of D1 receptor and hyperstimulation of D2 are respectively responsible for negative and
39 positive symptoms of schizophrenia (Jones & Buckley, 2006). This hypothesis has been refined and we
40 know that there are many other receptors involved in schizophrenia. Accurate classification of the drugs
41 could extend to receptor blockade profiles. This is crudely undertaken by grouping pharmacologically
42 (phenothiazines, butyrophenones etc.) but, once indexing is accurate and the receptor targeting known,
43 each compound could be given receptor weighting. Modelling these to the trial clinical outcomes could
44 generate hypothesis for new drug design.
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49 Furthermore, we suggest that the classification of pharmacological agents should not be binary – or
50 monothetic in classification terminology – and that these interventions fit better a fuzzy classification
51 system (G. Bowker, 1998) because of their pharmacological action on two or more receptors with
52 different percentage of occupancy in each type of receptor.
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3 Critics of Cochrane reviews often cite the production time as a problem (Turner et al., 2017) with good
4 reason. On average, it takes 2.4 years to conduct a Cochrane review with eight hours for screening every
5 1000 search results (Higgins & Green, 2011). A comprehensive specialized study-based database with
6 classified indexing makes it possible to run searches within seconds and gain only relevant results
7 (Shokraneh & Adams, 2019).
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10 It is commonly supposed that searching for pharmacological interventions is more straightforward than
11 non-pharmacological interventions. This probably remains true but, certainly, Information Professionals
12 should spend more time developing systematic searches for medications especially if they are dealing
13 with a class of drugs. Using a combination of sources and consulting experts may reduce the risk of
14 missing relevant drugs or their synonyms.
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17 FS invested much time in testing various options whilst developing the practical classification system
18 described above. Many mistakes were made which it is hoped, this paper will go some way to help
19 others avoid. Only one third of tested treatments for people with schizophrenia are drugs. Non-
20 pharmacological interventions are more common. The next classification effort should target non-drug
21 therapies.
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24 To avoid more chaos in knowledge organization by adding a new classification system (G. C. Bowker &
25 Star, 1999), we tried to rely on existing classification systems – at least initially. We found that the
26 current systems to be useful but, predictably, imperfect. Suggestions for improving existing
27 classifications are 1. Shorten the lag-time to update the classification system as much as possible,
28 missing new effective interventions may cost lives; 2. Include old interventions, some may be effective
29 but have not been reported on recently and are at risk of becoming forgotten; 3. Focus also on qualifiers
30 of interventions and fuzzy classes of drugs rather than binary classes of drugs.
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34 Limitations

35 We developed the methods for creating this classification during the maintenance of our register. We
36 faced problems during developing methods and so suggested and followed the practical solutions. There
37 might be important sources of drug information that we may have missed and using them may be
38 valuable. If any of the readers identify such sources, we encourage them to write to us or to write a
39 letter to the editor to inform the community.
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43 We have taken a comprehensive approach in including all schizophrenia RCTs regardless of their
44 language, date of publication, types of the documents, or publication status. However, we acknowledge
45 that searches within databases may not be accurate and we are unable to search all information sources
46 in all languages. It is likely that we have missed some trials.
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49 Regardless of the constant double and triple checking of the content and classification in our register by
50 our information specialist, we always have the possibility for human errors. However, this is a living
51 database and living classification system. When a new intervention or their qualifier is being added to
52 the register we have to check and amend the new concept to all new and old content in the database. It
53 is likely that the items of our classification that may change across time, probably especially for
54 qualifiers because, currently, there is no universal standard or consensus.
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Conclusion

Identification and classification of pharmacological interventions from trials requires use of many sources of information none of which are inclusive of all drugs. The limitations of each source is helpful to understand. Classification of non-pharmacological interventions is now a priority for clinical and information scientists and professionals (Roberts, Shokraneh, Sun, Groom, & Adams, 2020). Our classification led to several impact points that could be helpful for the future works to follow or adapt in similar works by information professionals.

Impact

On 17th December 2019, we shared the missing pharmacological interventions from WHO ATC to its developers at WHO Collaborating Centre for Drug Statistics Methodology in Norwegian Institute of Public Health.

Up until today (28 February 2020), this classification effort has detected new comparisons for review titles, new classes of drugs, and new qualifiers from existing RCTs. These discoveries were assessed by Cochrane editors and led to start and, in some cases, accomplishment of at least 14 Cochrane reviews: six on qualifiers (Abbas et al., 2017; Hanafi et al., 2017; Latifeh, Mohsen, Mohamad, & Nassif, 2019; Turk, Alkhatib, et al., 2017; Turk, Zuhri Yafi, et al., 2017; Turkmani et al., 2019), one on a class of drugs (Karl, Bergman, Abd El Sayed, & Adams, 2018), and nine on comparing two drugs (Bazrafshan, Zare, Okhovati, & Shamsi Meimandi, 2015; Chattopadhyay, Frey, & Green, 2016; Eslami Shahrababaki, Dehnavieh, Vali, & Sharafkhani, 2018; Ibragimov, Keane, Carreño Glaría, Cheng, & Llosa, 2019; Mazhari et al., 2017; Nikvarz, Vahedian, & Khalili, 2017; Nur & Adams, 2016; Schmidt, Phelps, Friedel, & Shokraneh, 2019; Zare & Bazrafshan, 2017).

Data sharing and online appendix

Following the call for sharing data from Cochrane Collaboration's work (Shokraneh et al., 2018), the data produced as the results of current classification activity is available via the following permanent link under CC-BY Attribution 4.0 International License (F. Shokraneh & C.E. Adams, 2020):

<https://doi.org/10.17605/OSF.IO/SXPC7>

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Table Legends

Table 1: Development status of drugs

Table 2: Classification of pharmacological interventions as described in Cochrane schizophrenia reviews

Table 3: Development status of pharmacological interventions from schizophrenia RCTs

Table 4: Non-WHO marketed pharmacological agents from Schizophrenia RCTs (sorted by clinical class)

Table 5: Classes of pharmacological interventions in schizophrenia RCTs

Table 6: Qualifiers of pharmacological interventions used in Cochrane Schizophrenia systematic reviews or RCTs

For Peer Review

Classification of all pharmacological interventions tested in trials relevant to people with schizophrenia: A study-based analysis

True ignorance is not the absence of knowledge, but the refusal to acquire it.

Karl Popper

I have neither the ability, knowledge, time, or space to classify all present-day therapies. All I feel capable of is a rough classification ...

Archie Cochrane

Abstract

Background: Systematic reviews ~~is are a~~ time-consuming, and resource-intensive ~~consuming process~~. Information Specialists are maintaining study-based registers to facilitate efficient conduct of ~~these types of~~ systematic reviews. Classification of study-level meta-data -such as interventions -can result in much more accurate searches, saving time in the early steps of systematic reviewing.

Objective: To classify all pharmacological interventions from all schizophrenia trials.

Methods: We used Cochrane Schizophrenia's Study-Based Register as the source of trials, Emtree and MeSH for synonyms, AdisInsight and CT.gov for research drugs, and WHO ATC for marketed drugs.

Results: One third of tested interventions on patients with schizophrenia are pharmacological (816; belonging to 106 clinical classes) with antipsychotic drugs being the most researched (15.1%). Only 528 of these medications are listed in WHO ATC. Around one third of these drug interventions are seen only in research (236; from 21 pharmacological/biochemical classes). Within the pharmacological interventions we identified 28 'qualifiers' including dose, route, and timing of drug delivery.

Conclusion: Identification and classification of pharmacological interventions from trials requires use of many sources of information none of which are inclusive of all drugs. Limitations of each source is helpful to understand. Classification of non-pharmacological interventions is now a priority for clinical and information scientists and professionals.

Keywords

Study-Based Registers; Classification; Schizophrenia; Randomised Controlled Trials; Systematic Reviews; World Health Organization; Pharmacological Interventions; Cochrane Collaboration; The Anatomical Therapeutic Chemical (ATC) Classification System

Key Messages for Practice

- There is no comprehensive resource to index/classify pharmacological interventions. Consider using a combination of resources to identify drug terms and drug classifications.
- WHO ATC has gaps for new drugs and regional pharmacological interventions from non-English speaking world - specifically drugs discovered/used in Japan.
- Practice of searching based on the *known* drug names and synonyms may not retrieve all the relevant studies - but only most relevant studies from the English-speaking world.

Background

To test the effects of new drugs, researchers often use the randomised controlled trial (RCT) study design. In these studies, participants are randomly assigned to different treatment groups. After a period of follow-up, outcomes are compared (Clarke et al., 2019). Related studies are often repeated to increase the certainty and applicability of findings. All relevant evidence from trials helps inform policy and clinical decisions and systematic reviews of the RCTs help this happen. To *conduct* a systematic review researchers follow a process that may include some or all these steps (Higgins & Green, 2011):

1. Searching all relevant databases;
2. Screening the title and abstract of search results for review eligibility;
3. Obtaining full reports of potentially eligible search results;
4. Screening full reports to identify the included studies;
5. Concatenating multiple reports of the same study to avoid multiple counting;
6. Extracting quantitative and qualitative data from included studies;
7. Analysing data; and
8. Writing the final report.

Information Specialists' involvement in systematic reviewing improves the quality of searches (Koffel & Rethlefsen, 2016; Meert, Torabi, & Costella, 2016). During the past 25 years – with the development of specialised registers in the Cochrane Collaboration – the role of some of the Information Specialists has developed beyond searching to involve screening and the development of subject-specific reference-based bibliographic registers of RCTs (Metzendorf & Featherstone, 2018). Furthermore, emergence of study-based registers, a sub-type of specialised registers, extended the Information Specialists' role to include data science expertise (Shokraneh & Adams, 2019). In study-based registers, all references or reports of the same study are linked to their study record – the meta-record (Shokraneh & Adams, 2017). This meta-record contains data about the study e.g. health care condition, interventions, outcomes (so called PICO) (Shokraneh, 2016). It is then possible to search *study* fields (e.g. health-care condition, such as interventions, -outcomes – so-called PICO (Shokraneh, 2016)) in addition to reference fields (e.g. title, abstract, etc.). If the reference-based registers were like a stack of books in one subject area with no classification, a study-based database could be compared to an organised library with a classification system based on PICO (Shokraneh & Adams, 2019). For this level of organisation to be

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3 useful, however, PICO meta-data has to be extracted from the full text reports of each study using
4 existing or new controlled vocabularies (**Figure 1**).
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6 **Figure 1:** Study-Based Register versus Reference-Based Register

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10 While Medical Subject Headings (MeSH), Excerpta Medica Tree (Emtree), and other controlled
11 vocabularies are used to assist information retrieval, a rigorous classification based on the PICO meta-
12 data has not yet been published. This paper addresses this deficit for pharmacological interventions ('I
13 in PICO) relevant to people with schizophrenia. Such classification can improve the performance of an
14 any information retrieval system and increase the relevancy of search results (Ingwersen & Järvelin,
15 2005) that may result in the need for minimum effort in screening search results. Using a classification
16 system to code studies with their PICO elements means that, the Information Specialist can complete
17 the first five steps outlined above before they are given to the reviewers, saving time in the overall
18 process (waste-reduction)Then, by the time a review team is supplied with studies, the Information
19 Specialist has completed the first five steps outlined above and the time-saving (waste-reduction) is
20 considerable (Shokraneh & Adams, 2019).
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26 **Objective**

27 To develop, and share learned lessons, and to make public the classification of pharmacological
28 interventions from the comprehensive study-based register of schizophrenia RCTs.
29

30 **Audience**

31 Those who deal with classification of interventions in any context. We, however, followed the
32 recommendation by knowledge organisation theoreticians to keep the classification within its context
33 (G. C. Bowker & Star, 1999) and intentionally remind the reader that this classification was born out of
34 systematic reviews and a specialised trials register and wider generalisation would need to be tested.
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38 We have used the terms drug, medication, and pharmacological intervention interchangeably and as
39 synonyms.
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44 **Methods**

45 **Source of data: Cochrane Schizophrenia Group's Study-Based Register of Trials**

46 This database was started nearly 30 years ago (Adams & Gelder, 1994) to facilitate the systematic
47 review process in the Cochrane Schizophrenia Group. Currently, it supports running the searches for
48 over 324 maintained Cochrane reviews (increasing at rate of 25-30/year). This database is being
49 maintained using the MeerKat 1.6 computer program and details of this register are described
50 elsewhere (Cochrane Schizophrenia Group, 2019; F. Shokraneh & C.E. Adams, 2020).
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Timeline and resource

This research took place between 17 December 2014 and 6 January 2019 by a full-time Information Specialist.

Piloting

In December 2014, the database already contained 9200 intervention labels for the approximately 18,500 trials. It seemed unlikely that a new intervention was tested in every second study. Investigating only interventions starting with the letter 'A' showed that over half were duplicates undetected by the machine software because of:

- (Human) errors in spelling;
- Differences between American and British spelling;
- Unique entry of synonyms/brand names rather than use of generic name;
- Indexing aspects of *administration* or *actions* rather than the drug itself.

Despite the attempted development of a standard protocol for indexing PICO meta-data in April 2004 as part of the PsiTri project (EU-PSI Coding Manual Working Group, 2004) there was clearly a problem in consistency. This may have happened because of changes in geography or human resources or infrastructures that the organisation loses knowledge or a process (G. C. Bowker, 1997) usually unintentionally – so-called organizational forgetting (de Holan, Phillips, & Lawrence, 2014).

Data cleaning

To solve these problems, FS corrected spelling errors, separated the interventions from intervention qualifiers (subheadings) and made sure a single preferred controlled term was employed instead of multiple synonyms of the same drug. The project then required development of a classification system in order to facilitate the process of systematic reviewing.

Current subjective classification in titles of Cochrane reviews

FS initially relied on the author-led classification within Cochrane Schizophrenia's existing systematic reviews. These 324 reviews, although the largest sample of maintained systematic reviews in existence, still cover only a subset of pharmaceutical approaches tested in all schizophrenia trials. Currently, classification from titles would generate many omissions. In addition, even within these titles, there are inconsistencies and synonyms. Clearly, a classification system was needed.

Choice of objective tools

FS investigated AdisInsight, Emtree, MeSH, British National Formulary (BNF), and WHO Anatomical Therapeutic Chemical classification system (WHO ATC) for their indexing of drugs starting with the letter 'A'.

- AdisInsight - the most comprehensive source for recent research drugs (sourcing part of its data from ClinicalTrials.Gov);
- BNF - suggested practical *clinical* classes for some drugs but coverage was very limited.

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- 3 - Emtree and MeSH - solely useful in identifying different synonyms of old research drugs because
- 4 of their longevity - not good at identifying drugs used outside Western Europe and the English
- 5 speaking world;
- 6
- 7 - WHO ATC - the best available classification option for approved, marketed drugs;
- 8

9 None of these tools covered all 'A' drug interventions in the register of trials. Because it is a priority for
10 Cochrane reviews to support clinical practice, the decision was taken to use WHO ATC. FS indexed every
11 compound with the generic drug name, assigned WHO ATC code, the clinical class and pharmacological
12 action class or chemical structure/group class. Where the intervention in the RCT referred to more than
13 one drug (i.e. a class of drugs), FS used an asterisk after the term to indicate this (see Online Appendix).
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16 Sources of synonyms and identifying non-marketed drug names

17 During a drug's life cycle, a drug may have a chemical name, research names, a generic name and brand
18 names. These names also reflect different phases of drug development (Scutti, 2016). Although WHO
19 ATC is the most comprehensive source of classification of marketed drugs, it does not support searches
20 for synonyms. FS, therefore, used Emtree (inclusive of MeSH terms) for this and, in all cases, recorded
21 the generic name. Thereafter FS used WHO ATC to find the drug's class name, tree and number.
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24 For drugs not in the WHO ATC:

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- 27 1. AdisInsight was used to cover recent drugs in RCTs; then
- 28 2. ClinicalTrials.Gov searched to cover recent drugs not in AdisInsight; then
- 29 3. Google searched (inclusive of Google Books) to cover old drugs; and finally
- 30 4. Classes suggested/claimed within the RCT reports used to cover drugs unclassified in other
31 sources.
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34 For a *marketed* drug not within WHO ATC, the same data as for marketed drugs were recorded, with the
35 nearest possible WHO ATC code and the uncertainty in last digits and letter was expressed by use of
36 question marks '?' to indicate unknown digits and letters that are pending and to be assigned by WHO
37 ATC.
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40 Drugs not on the market and their development status

41 We considered a drug to be a 'drug only used in research' if it met the following criteria:

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- 44 • Not listed in WHO ATC; and
- 45 • Despite searching current major relevant resources, no wider/generic reference to the drug was
46 identified.
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49 During the indexing process, FS recorded the last used name of the drug, development status, potential
50 clinical class, and potential pharmacological action or chemical structure/group (**Table 1**).
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Please insert Table 1

Double-checking

During cleaning of data it became clear that some interventions were missing from the original Cochrane Schizophrenia Group's Register's study records. Human errors are inevitable in a task of this size but these errors make searches unreliable. FS double-checked all indexing and, in the case of discrepancy or complexity, consulted a specialist psychiatrist.

Indexing principles

We indexed what interventions patients had been *randomised to*- although this was not always straightforward. For example, sometimes participants were randomised to a combination of drugs or two different doses of the same drug. In these cases we applied qualifiers as we had learnt was necessary from our pilot study above. We also tried to follow the indexing principles:

- *Literary Warranty* (Rodriguez, 2008): the drug enters the classification system if it has been used in one of the treatment arms (or as part of the randomised treatment) in one or more RCTs.
- *Co-ordination* (Bachrach & Charen, 1978): when impossible to describe an intervention using a single index term more than one concept or qualifiers were used to describe the intervention.
- *Multiplicity* (Bachrach & Charen, 1978): indexing covered all interventions in the randomised arms- even if the drug was not specific or was not a major part of the treatment.
- *Specificity* (Bachrach & Charen, 1978): indexing focused on the most specific intervention rather than broad classes.

In rare cases pragmatic decisions had to be made. For example, where researchers have randomised people to a *class* of drugs—without naming the specific compounds—drug-level indexing was impossible.

Theoretical context for current classification

As a result of using WHO ATC, which is updated centrally and is stable, the classification scheme partly followed the Practicalist approach to knowledge organization (Hjørland, 2016b). However, the classification used by the *systematic reviewers* for Cochrane reviews follows a expert-agreed consensus-based approach (Hjørland, 2016b). Also, we utilized a facet-analytic approach as the intervention classification also involved drug 'facets' – such as route of administration, dosage, and, in some cases, flavour or colour. Many trials use a combination of interventions and some compare an aspect or facet of one intervention (i.e. oral form versus injection of the same drug). This approach has the advantage of being the 'most explicit' and a 'pure theoretical approach' (Hjørland, 2016a) but we also found it practical when it came to classification of facets in trial comparisons.

Results

Existing classification within the systematic reviews

After nearly 30 years of working, still only 10% of RCTs have been included in systematic reviews produced by the Cochrane Schizophrenia Group – but, limited though this is, these trials are likely to

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3 represent a subset of comparisons that are considered important by clinicians, policy makers,
4 researchers and consumers of care. This was the starting point for the classification of pharmacological
5 interventions (summarised in **Table 2**) and identified 19 classes of drugs. Thirteen classes, however,
6 were based on pharmacological action of drugs, three on clinical action and the last three based on
7 chemical group/structure.
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10 **Please insert Table 2**

13 One third of tested schizophrenia treatments are drugs

14 After cleaning 9,200 interventions, 2,792 remained unique. About one third (816) are pharmacological
15 interventions 71% of which are on the market (**Table 3**).
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19 **Please insert Table 3**

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23 Most of these pharmacological interventions (65%) have been classified in WHO ATC (528 drugs).
24 However, an additional 52 drugs were not present in WHO ATC but are in the market (**Table 4**). Most of
25 these 52 are used as chemical food additives; however, some were country-specific drugs such as
26 Blonanserin, Spiperone, Perospirone, and Timiperone (Japan).
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30 **Please insert Table 4**

35 WHO ATC classes

36 There are 13 major anatomical categories in WHO ATC and, predictably, most of the drugs in the
37 Cochrane Schizophrenia Register belong to the 'Nervous System Drugs' (49.3 %). At the finer 'clinical
38 class' level, these drugs belong to 106 classes – with the antipsychotics being the most researched
39 (15.1%). WHO ATC also provides a 'pharmacological action and/or chemical structure' class (**Table 5**).
40 Drugs may affect more than one receptor and have more than one pharmacological action. FS grouped
41 the major pharmacological mechanism of action of research drugs into 21 major categories of either
42 pharmacological action or biochemical group. Over 40% of research drugs target one or more of
43 Serotonin, Dopamine, Acetylcholine, and GABA A receptors.
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48 Considerations when using the WHO ATC

49 False 'classes' such as atypical/typical or first/second generations antipsychotics were not listed in WHO
50 ATC - unlike the International Classification of Diseases (ICD) where the industry – insurance companies,
51 industrial firms, and pharmaceutical companies – had an influence on the classification (G. Bowker &
52 Star, 1991). ~~It is only for cephalosporins (a class of antibiotics) that use of 'generations' is relevant and~~
53 ~~valid.~~
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Although WHO ATC is currently the best available classification for our purpose, it does have important known limitations (Merabti et al., 2011) and ~~we added with the following our study found some more:~~

- Duplicates: WHO ATC contains many duplicates. This is not only where a drug is classed - justifiably - in two places but genuine duplication of the same drug appearing in the search results more than once with the same class code.
- No ordered hierarchy: For example, after the overarching anatomical class, the next class down is sometimes clinical, sometimes pharmacological and sometimes a chemical structure or group.
- Listed drugs limited by assignment to anatomical class: For example, a drug listed under 'ophthalmologicals' is being used by people with schizophrenia not because of this anatomical class but because of its pharmacological (anticholinergic) action. As a result, the anatomical classification will appear odd for those using the classification for condition-specific indexing.
- Synonyms: It is not possible to search synonyms of drugs.
- Spelling: WHO ATC relies on a European spelling of the generic drug name (i.e. amfetamine not amphetamine) and there is no function to recognise potential differences in spelling when searching.
- Different binders of the same drug not covered: For example, the important distinction between Zuclopenthixol *acetate* and Zuclopenthixol *decanoate* is not made.
- Marketed drugs: WHO ATC largely – but not entirely comprehensively (see below) – relies on drugs already at market. It does not list experimental or upcoming drugs or classes.
- Geographical bias: it is largely based on drugs from Western countries.

Please insert Table 5

Qualifiers (subheadings)

The most frequently used 'qualifiers' from the perspective of systematic reviews were used to develop the main set employed in the final classification (**Table 6**).

Please insert Table 6

One third of tested schizophrenia drugs are not on the market

The ~~development status of re-were~~ 236 of pharmacological interventions ~~were~~ 'developing', or in 'unclear development state' or 'stopped' (29% of ~~RCT-tested-reported~~ schizophrenia drugs ~~in RCTs~~). The majority of research drugs were targeting nervous system and were purported antipsychotics, anti-Parkinson agents, and antidepressants. The clinical purpose of 65 of these drugs (27.5%) is not available.

As available in the **Online Appendix**, only 19 of these drugs (8%) were withdrawn post-marketing (Methitural, Phencyclidine, Benzquinamide, Flurothyl, Lysergic Acid Diethylamide (LSD), Picrotoxin,

Benactyzine, Etryptamine, Pheniprazine, Azacyclonol, Carphenazine, Mepazine, and Piperacetazine). The rest either are still being researched, stopped, or are in unclear development state.

The new learned lessons

We already discussed the benefits of a study-based register for preventing errors in systematic reviewing (Shokraneh & Adams, 2019; Shokraneh & Adams, 2017). However, this study has uncovered two additional errors that could be prevented because of the use of a study-based register with a classification system:

- *Out-of-date status of studies:* it is easy for systematic reviewers to misclassify the status of the study as 'ongoing' - where details are incomplete and not enough to include or exclude a study in a review - without the full availability of all reports of a study. Through standardisation of the interventions we merged many what we had previously thought of as separate studies into one study. As a result, status of some studies changed from 'ongoing' to 'completed'. The better indexing resulted in more accurate concatenation and complete study records so that a more informed decision could be made about how to use the study data within the review.
- *Exclusion because of unknown intervention names:* systematic review authors search for all drug names known to them. They (and Information Specialists working with them) are unaware of the unknown names of the same drug~~systematic review authors search for all known drug names—as they—and even the Information Specialists working with them—are unaware of the unknown names of the same drug.~~ Clearly, there are names for even very widely used compounds that are unfamiliar to many. Use of generic names for indexing, at the study level, helps avoid failing to identify studies which originate from places using very unfamiliar drug names. For example, 'ditan' is one brand name for 'diazepam' *and* several other drugs (!). It is not mentioned in MeSH or Emtree as entry term under any drug. It is also the name of a traditional Chinese medicine. To further confuse matters, 'ditans' refers to a class of drugs in the 'Western' medicine. After detailed investigation we identified that the intervention 'ditan' was a brand name for 'diazepam' employed in far East. The 'ditan' RCT which had been missing from assessment in the published review on benzodiazepines~~After much research, and confusion, we identified that the intervention 'ditan' was a brand name for 'diazepam' employed in far East. This 'ditan' RCT had been missing from assessment in the published review on benzodiazepines~~ (Dold et al., 2012) was then identified and added to the ongoing update of the review.

Discussion

This research is the first effort to classify pharmacological interventions tested within a defined group of RCTs. The source of RCTs – the Study-Based Register of the Cochrane Schizophrenia Group – has coverage from 1949 (the date of the very first relevant RCT (Kitzinger, Arnold, & et al., 1949)) to the present and contains any published or unpublished document regardless of type or language. Accessing this comprehensive database affords opportunity to categorise all drugs tested in one important corner

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3 of health care. Information Specialists with intimate knowledge of a certain medical speciality can
4 classify the relevant interventions and have the best chance in keeping abreast of the changing names of
5 drugs. Having said this, this study found important trials that had been buried in the register for over
6 two decades that had not been included in relevant reviews because the brand name of the drug was
7 unknown in Western medicine.
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10 The number of drugs tested for people with schizophrenia was impressive. Certainly, the heterogeneous
11 pharmacogenetic profile of patients, the different states and stages of psychosis (Lieberman & First,
12 2018), the varying symptom profiles of schizophrenia (Steeds, Carhart-Harris, & Stone, 2015), and co-
13 morbidities (iatrogenic and otherwise) all have added to the need for a long list of medications used for
14 treating schizophrenia. However, probably the greatest driver for developing and testing alternative
15 drugs is that, although the drugs are effective, they are far from perfect. For example, although
16 effective, antipsychotics are widely disliked due to their side effects and because they unpleasant to
17 take/administer. They may be only partially effective leaving the person experiencing new adverse
18 effects along with old half-responsive psychotic symptoms. The number of drugs may reflect not only
19 the complexity of the illness or illnesses, but also the vigour of the search for a better treatment for this
20 most difficult of conditions.
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25 We concur that classifications should be used in their own context (G. Bowker, 1998). We identified
26 many medications in WHO ATC with anatomical classes *irrelevant* to schizophrenia yet the
27 pharmacological action was relevant. Our classification system was developed to be used in the context
28 of interventions from trials of people with schizophrenia. Any use for other purposes may require
29 modifications. The materials used as the source of interventions were the RCTs reported by medical
30 researchers and the classification systems used to standardize the collected interventions – just like
31 other medical classification systems – were not necessarily designed based on clinicians' or systematic
32 reviewers' needs (G. Bowker & Star, 1991). For example, WHO ATC classifies 'Lithium' as an
33 antipsychotic drug but no systematic review of antipsychotic drugs includes 'Lithium'. Reviewers
34 consistently refer to lithium as a 'Mood Stabilizer' - a class of drugs that has no place in WHO ATC. In
35 some cases, to meet both WHO ATC class and reviewers' need, we kept both classes working in parallel.
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41 **Are systematic reviewers also good classification developers?**

42 Although the Cochrane review titles – developed following PICO framework – were a good starting point
43 for identifying important classes of interventions, it is clear that the systematic reviewers have not
44 followed a standard classification system when choosing terminology for review titles. Some titles are
45 based on clinical class, others on pharmacological class, and, in some cases, there were duplicate terms
46 for describing the same concept (i.e. typical antipsychotics and first generation antipsychotics); the
47 latter concept being not a true class of drug but more one imposed by industry with pecuniary interests.
48 It is not clear that the titling of Cochrane reviews has to be this inconsistent. It is important to
49 communicate clearly the target of the review in terms that make the work easy to identify and access. In
50 this, classification can help. It may be that, in general, the title of the Cochrane review should use
51 generic drug names or pharmacological classes as default. Titling of a Cochrane Overview (a review of
52 reviews), however, may be best to favour either pharmacological classes or/and clinical class.
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What qualifies as qualifier?

Until now, no classification system has considered useful qualifiers of pharmacological interventions. We had to develop the list of qualifiers for both existing reviews and, looking to the future, as yet un-reviewed RCTs. We considered a concept/aspect as a 'qualifier' when people were randomised to an 'aspect' or facet of the same drug – for example timing of when the same drug is given, or generic vs. trade forms of the same compound. Before the end of this classification effort, there was little information on what aspects of the drugs have been targeted and tested in RCTs. Now we are aware that many have been tested - from the size and flavour of pill to the depth of injection – and that these qualifiers can also be the focus new systematic reviews.

Marketed non-WHO ATC drugs

There are marketed schizophrenia drugs in China, Czech Republic and Japan that are not listed in WHO ATC. These omissions may reflect some degree of a language barrier to entry on WHO ATC. A highly specific indexing project such as this one is able to identify such omissions but is also vulnerable to them. For example, Japan's ICHUSHI – historically, the second medical bibliographic database after MEDLINE and having 12 million records – is currently inaccessible to Cochrane Schizophrenia Group and may contain more trials of other drugs unknown to us. With illnesses such as schizophrenia, for which care must be tailored depending on many variables including individual response – however idiosyncratic – every potential drug treatment is an important addition to the armoury.

One third of schizophrenia drugs are not on the market

Overall, there was poor reporting of the reasons why drugs had not reached the market. Where AdisInsight reported that a drug had ceased being tested, it gave no reason. It may be that these drugs were ineffective or toxic. This should be reported to prevent more trials. Other drugs may have been effective but not been brought to market for reasons of finance, business strategy (Bannister, Adams, & Shokraneh, 2019), or organisational forgetting during the merger of pharmaceutical companies. This also should be made clear for as the chemical is off-patent it could be made available again as another treatment for this difficult illness.

Receptors targeted by non-marketed drugs

There could be benefits to study retrieval if receptor blockage profiles were classified alongside drugs. The dopamine (D) hypothesis, accepted among many schizophrenia researchers, explains that hypostimulation of D1 receptor and hyperstimulation of D2 are respectively responsible for negative and positive symptoms of schizophrenia (Jones & Buckley, 2006). This hypothesis has been refined and we know that there are many other receptors involved in schizophrenia. Accurate classification of the drugs could extend to receptor blockade profiles. This is crudely undertaken by grouping pharmacologically (phenothiazines, butyrophenones etc.) but, once indexing is accurate and the receptor targeting known, each compound could be given receptor weighting. Modelling these to the trial clinical outcomes could generate hypothesis for new drug design.

Furthermore, we suggest that the classification of pharmacological agents should not be binary – or monothetic in classification terminology – and that these interventions fit better a fuzzy classification

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3 system (G. Bowker, 1998) because of their pharmacological action on two or more receptors with
4 different percentage of occupancy in each type of receptor.
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6 Critics of Cochrane reviews often cite the production time as a problem (Turner et al., 2017) with good
7 reason. On average, it takes 2.4 years to conduct a Cochrane review with eight hours for screening every
8 1000 search results (Higgins & Green, 2011). A comprehensive specialized study-based database with
9 classified indexing makes it possible to run searches within seconds and gain only relevant results
10 (Shokraneh & Adams, 2019), ~~almost eliminating the title and abstract screening time.~~
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14 It is commonly supposed that searching for pharmacological interventions is more straightforward than
15 non-pharmacological interventions. This probably remains true but, certainly, Information Professionals
16 should spend more time developing systematic searches for medications especially if they are dealing
17 with a class of drugs. Using a combination of sources and consulting experts may reduce the risk of
18 missing relevant drugs or their synonyms.
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21 FS invested much time in testing various options whilst developing the practical classification system
22 described above. Many mistakes were made which it is hoped, this paper will go some way to help
23 others avoid. Only one third of tested treatments for people with schizophrenia are drugs. Non-
24 pharmacological interventions are more common. The next classification effort should target non-drug
25 therapies.
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28 To avoid more chaos in knowledge organization by adding a new classification system (G. C. Bowker &
29 Star, 1999), we tried to rely on existing classification systems – at least initially. We found that the
30 current systems to be useful but, predictably, imperfect. Suggestions for improving existing
31 classifications are 1. Shorten the lag-time to update the classification system as much as possible,
32 missing new effective interventions may cost lives; 2. Include old interventions, some may be effective
33 but have not been reported on recently and are at risk of becoming forgotten; 3. Focus also on qualifiers
34 of interventions and fuzzy classes of drugs rather than binary classes of drugs.
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38 Limitations

39 We developed the methods for creating this classification during the maintenance of our register. We
40 faced problems during developing methods and so suggested and followed the practical solutions. There
41 might be important sources of drug information that we may have missed and using them may be
42 valuable. If any of the readers identify such sources, we encourage them to write to us or to write a
43 letter to the editor to inform the community.
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47 We have taken a comprehensive approach in including all schizophrenia RCTs regardless of their
48 language, date of publication, types of the documents, or publication status. However, we acknowledge
49 that searches within databases may not be accurate and we are unable to search all information sources
50 in all languages. It is likely that we have missed some trials.
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53 Regardless of the constant double and triple checking of the content and classification in our register by
54 our information specialist, we always have the possibility for human errors. However, this is a living
55 database and living classification system. When a new interventions or their qualifier is being added to
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3 the register we have to check and amend the new concept to all new and old content in the database. It
4 is likely that the items of our classification that may change across time, probably especially for
5 qualifiers because, currently, there is no universal standard or consensus.
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10 Conclusion

11 Identification and classification of pharmacological interventions from trials requires use of many
12 sources of information none of which are inclusive of all drugs. The limitations of each source is helpful
13 to understand. Classification of non-pharmacological interventions is now a priority for clinical and
14 information scientists and professionals (Roberts, Shokraneh, Sun, Groom, & Adams, 2020). Our
15 classification led to several impact points that could be helpful for the future works to follow or adapt in
16 similar works by information professionals.
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20 Impact

21 On 17th December 2019, we shared the missing pharmacological interventions from WHO ATC to its
22 developers at WHO Collaborating Centre for Drug Statistics Methodology in Norwegian Institute of
23 Public Health.
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26 Up until today (28 February 2020), this classification effort has detected new comparisons for review
27 titles, new classes of drugs, and new qualifiers from existing RCTs. These discoveries were assessed by
28 Cochrane editors and led to start and, in some cases, accomplishment of at least 14 Cochrane reviews:
29 six on qualifiers (Abbas et al., 2017; Hanafi et al., 2017; Latifeh, Mohsen, Mohamad, & Nassif, 2019;
30 Turk, Alkhatib, et al., 2017; Turk, Zuhri Yafi, et al., 2017; Turkmani et al., 2019), one on a class of drugs
31 (Karl, Bergman, Abd El Sayed, & Adams, 2018), and nine on comparing two drugs (Bazrafshan, Zare,
32 Okhovati, & Shamsi Meimandi, 2015; Chattopadhyay, Frey, & Green, 2016; Eslami Shahrabaki,
33 Dehnavieh, Vali, & Sharafkhani, 2018; Ibragimov, Keane, Carreño Glaría, Cheng, & Llosa, 2019; Mazhari
34 et al., 2017; Nikvarz, Vahedian, & Khalili, 2017; Nur & Adams, 2016; Schmidt, Phelps, Friedel, &
35 Shokraneh, 2019; Zare & Bazrafshan, 2017).
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40 Data sharing and online appendix

41 Following the call for sharing data from Cochrane Collaboration's work (Shokraneh et al., 2018), the data
42 produced as the results of current classification activity is available via the following permanent link
43 under CC-BY Attribution 4.0 International License (F. Shokraneh & C.E. Adams, 2020):
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46 <https://doi.org/10.17605/OSF.IO/SXPC7>
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Table Legends

Table 1: Development status of drugs

Table 2: Classification of pharmacological interventions as described in Cochrane schizophrenia reviews

Table 3: Development status of pharmacological interventions from schizophrenia RCTs

Table 4: Non-WHO marketed pharmacological agents from Schizophrenia RCTs (sorted by clinical class)

Table 5: Classes of pharmacological interventions in schizophrenia RCTs

Table 6: Qualifiers of pharmacological interventions used in Cochrane Schizophrenia systematic reviews or RCTs

For Peer Review

Table 1: Development status of drugs

Development Status		Description
<i>Currently marketed for clinical practice</i>	WHO	Listed in WHO ACT.
	Non-WHO	Not listed in WHO ACT.
If not marketed		
<i>Drugs used in research†</i>	Developing-Adis	Status 'developing' in RCT cited in Adis Insight.
	Developing-CT.Gov	Status 'developing' in RCT cited in ClinicalTrials.Gov.
	Developing	Used as research drug after 2000 in at least one RCT.‡
If not marketed but clearly stopped		
<i>Stopped</i>	Stopped-Adis	Status 'stopped' in RCT cited in Adis Insight.
	Stopped-CT.Gov	Status 'stopped' in RCT cited in ClinicalTrials.Gov.
	Post-Marketing Withdrawal§	Originally marketed and then withdrawn from market.
	Stopped	Not used after 2000 in any RCT.
If not marketed, not researched, nor stopped		
<i>Unclear</i>	Unclear-Adis	No report of RCTs cited in Adis Insight.
	Not Available	No traceable evidence about the development state.
	Not Marketed	No traceable country of market.

†Drugs may have established use for other conditions.

‡We used the year 2000 as arbitrary break-point.

§'Market' refers to *legal* market for *humans* - some drugs are considered as illicit drugs, doping drugs (abused in humans and in horse-racing), and some are still being used in veterinary medicine.

Table 2: Classification of pharmacological interventions as described in Cochrane schizophrenia reviews

#	Class of Intervention	Nature of Class
1	Acetylcholinesterase inhibitors	Pharmacological Action
2	Amphetamines	Chemical Group/Structure
3	Anticholinergics	Pharmacological Action
4	Antidepressants	Clinical Action
5	Antiglucocorticoid and related treatments	Pharmacological Action
6	Antioxidants	Pharmacological Action
7	Antipsychotics	Clinical Action
7.1	Atypical antipsychotics=New generation antipsychotics	Clinical Action
7.1.1	Newer atypical antipsychotics	Clinical Action
7.2	Typical antipsychotics=First-generation antipsychotics	Clinical Action
7.2.1	Low-potency first-generation antipsychotics	Clinical Action
8	Benzodiazepines	Chemical Group/Structure
9	Beta-adrenergic-blocking agents (beta blockers)	Pharmacological Action
9.1	Central action beta-blockers	Pharmacological Action
10	Calcium channel blockers	Pharmacological Action
11	Gamma-aminobutyric acid agonists	Pharmacological Action
12	Glutamatergic drugs	Pharmacological Action
13	HMG-CoA reductase inhibitors (statins)	Pharmacological Action
14	Mood stabilisers	Clinical Action
15	Non-antipsychotic catecholaminergic drugs	Pharmacological Action
16	Polyunsaturated fatty acid supplementation	Chemical Group/Structure
17	Selective noradrenaline reuptake inhibitors	Pharmacological Action
18	Vesicular monoamine transporter inhibitors	Pharmacological Action

Table 3: Development status of pharmacological interventions from schizophrenia RCTs

Development status		Number (% of total)	
<i>Currently marketed</i> [†]	WHO	528 (65.0)	580 (71.1)
	Non-WHO	52 (6.4)	
<i>Drugs used in research</i> [‡]	Developing-Adis	33 (4.0)	45 (5.5)
	Developing-CT.Gov	5 (0.6)	
	Developing	7 (0.9)	
<i>Stopped</i>	Stopped-Adis	72 (8.8)	150 (18.4)
	Stopped-CT.Gov	1 (0.1)	
	Post-Marketing withdrawal [§]	13 (1.6)	
	Stopped	64 (7.8)	
<i>Unclear</i>	Unclear-Adis	29 (3.9)	277 (34.0)
	Not Available	25 (3.0)	
	Not Marketed	223 (27.3)	

Note: Drugs may appear in more than one category so there are overlaps among categories and percentages and numbers do not add up. Please refer to online Excel file for more details.

[†]Either for clinical practice or for use as products consumed by humans.

[‡]Research for the purpose of clinical practice for people with schizophrenia.

[§]'Market' refers to *legal* market for *humans* - some drugs are considered as illicit drugs, doping drugs (abused in humans and in horse-racing), and some are still being used in veterinary medicine.

Table 4: Non-WHO* marketed pharmacological agents from Schizophrenia RCTs (sorted by clinical class)

Intervention	Code	Clinical Class	Pharmacological Action/Chemical Class
Sydnocarb	N06B???	Agents Used for ADHD and Nootropics	Dopamine Uptake Inhibitors
Benserazide	N04BA??	Anti Parkinson Drugs	Dopaminergic Agents
Deutetrabenazine	N07XX??	Anti Parkinson Drugs	Vesicular Monoamine Transporter 2 Inhibitors
Hopantenic Acid	N04????	Anti Parkinson Drugs	Not Available
Mepiprazole	N05AX??	Antidepressants	Phenylpiperazine Derivatives
Tandospirone	N06AB??+ N05BE??	Antidepressants+Anxiolytics	Serotonin Reuptake Inhibitors
Latrepirdine	R06AX??	Antihistamines for Systemic Use	Acetylcholinesterase Inhibitors
Sulfadoxine	J01ED??	Antimalarials	Long-Acting Sulfonamides
Blonanserin	N05AX??	Antipsychotics	Not Available
Carpipramine	N05AD??	Antipsychotics	Butyrophenone Derivatives
Clocapramine	N05AX??	Antipsychotics	Imidobenzyl Derivatives
Clotepine(Clortepine)	N05AX??	Antipsychotics	Perathiepin Derivatives
Nemonapride	N05AL??	Antipsychotics	Benzamides
Oxyprothepin	N05AX??	Antipsychotics	Not Available
Perlapine	N05AH??	Antipsychotics	Diazepines, Oxazepines, Thiazepines and Oxepines
Perospirone	N05BE??	Antipsychotics	Azaspirodecanedione Derivatives
Spiperone	N05AD??	Antipsychotics	Butyrophenone Derivatives
Timiperone	N05AD??	Antipsychotics	Butyrophenone Derivatives
Delorazepam	N05BA??	Anxiolytics	Benzodiazepine Derivatives
Cereobiogen	A03AX??	Drugs for Functional Gastrointestinal Disorders	Not Available
Silicon Dioxide	A03AX13	Drugs for Functional Gastrointestinal Disorders	Not Available
Chromium Picolinate	A10X???	Drugs Used in Diabetes	Not Available
Lodenafil Carbonate	G04BE??	Drugs Used in Erectile Dysfunction	Phosphodiesterase Type 5 Inhibitors
Berberine	V06D???	General Nutrients	Not Available
Caffeic Acid	V06D???	General Nutrients	Not Available
Carnosine	V06D???	General Nutrients	Not Available
Epigallocatechin Gallate	V06D???	General Nutrients	Not Available
Essential Fatty Acids*	V06D???	General Nutrients	Not Available
Gamma-Aminobutyric Acid	V06D???	General Nutrients	Not Available
Gastrodin	V06D???	General Nutrients	Not Available
Glucuronolactone	V06D???	General Nutrients	Not Available
Lecithin	V06D???	General Nutrients	Not Available
Linoleic Acid	V06D???	General Nutrients	Not Available
Magnesium Glutamate	V06D???	General Nutrients	Magnesium Compounds
Magnesium Threonate	V06D???	General Nutrients	Not Available
Protoporphyrin Disodium	V06D???	General Nutrients	Not Available
Quercetin	V06D???	General Nutrients	Not Available
Saccharin	V06D???	General Nutrients	Not Available
Sodium Butyrate	V06D???	General Nutrients	Not Available

Sodium Glutamate	V06D???	General Nutrients	Amino Acids
Succinic Acid	V06D???	General Nutrients	Not Available
Tetrahydropalmitine	V06D???	General Nutrients	Not Available
Penehyclidine	N05CM??	Hypnotics and Sedatives	Anticholinergic Agents
Arginine Aspartate	B05XB??	I.V. Solution Additives	Amino Acids
Creatine	B05XB??	I.V. Solution Additives	Amino Acids
Phenylalanine	B05XB??	I.V. Solution Additives	Amino Acids
Taurine	B05XB??	I.V. Solution Additives	Amino Acids
Theanine	B05XB??	I.V. Solution Additives	Amino Acids
Tyrosine	B05XB??	I.V. Solution Additives	Amino Acids
Batyl Alcohol	V06D???	Not Available	Not Available
Levamlodipine Maleate	C08CA??	Not Available	Calcium Channel Blockers
Dydroprogesterone	G03????	Sex Hormones and Modulators of the Genital System	Selective Estrogen Receptor Modulators

* These drugs were shared with WHO ATC for being considered and – if found relevant – to be added to WHO ATC.

Table 5: Classes of pharmacological interventions in schizophrenia RCTs

Anatomical physiological systemic class	M	Clinical class		Pharmacological class			
		M	RD	M*	RD*		
Alimentary tract and metabolism	74	Acid related disorders drugs	12	0	Adrenergic receptor antagonists	0	3
Anti-infectives for systemic use	24	Addictive disorders drugs	7	1	Alkaloids	9	0
Anti-neoplastic and immunomodulating agents	12	ADHD drugs and nootropics	20	1	Amino acids	9	4
Anti-parasitic products, insecticides and repellents	8	Analgesics	19	1	Amino acids/monoamine oxidase inhibitors	0	6
Blood and blood forming organs	19	Anesthetics	15	2	AMPA receptor modulators	0	4
Cardiovascular system	61	Anti-bacterials	13	0	Antiadrenergic agents	11	0
Genito-urinary system and sex hormones	21	Anti-dementia drugs	7	4	Anticholinergic agents	18	3
Hormonal preparations, excl. sex hormones and insulins	10	Anti-depressants	43	12	Anticholinesterases	8	0
Musculo-skeletal system	11	Anti-emetics and anti-nausea drugs	0	1	Barbiturates	7	0
Nervous system	286	Anti-epileptics	19	3	Benzodiazepines	25	0
Respiratory system	18	Anti-histamines	8	0	Benzamides	8	0
Sensory organs	4	Anti-hypertensives	13	1	Beta blocking agents	14	0
Various	32	Anti-malarials	8	0	Butyrophenone derivatives	13	7
		Anti-mycobacterials	5	0	Calcium channel blockers	7	0
		Anti-neoplastics	0	1	Diazepines, oxazepines, thiazepines, oxepines	7	0
		Anti-obesity drugs	7	0	Dihydropyridinederivatives	6	0
		Anti-Parkinsonism drugs	27	17	Dopaminergic agents	15	35
		Anti-psychotics	80	113	Fatty acid derivatives	5	0
		Anxiolytics	18	6	GABA-a receptor modulators	0	10
		Constipation drugs	5	0	Glutamate receptor modulators	0	8
		Convulsants	0	1	Glycine transporter inhibitors	0	7
		Diabetes drugs	11	0	HMG CoA reductase	6	0

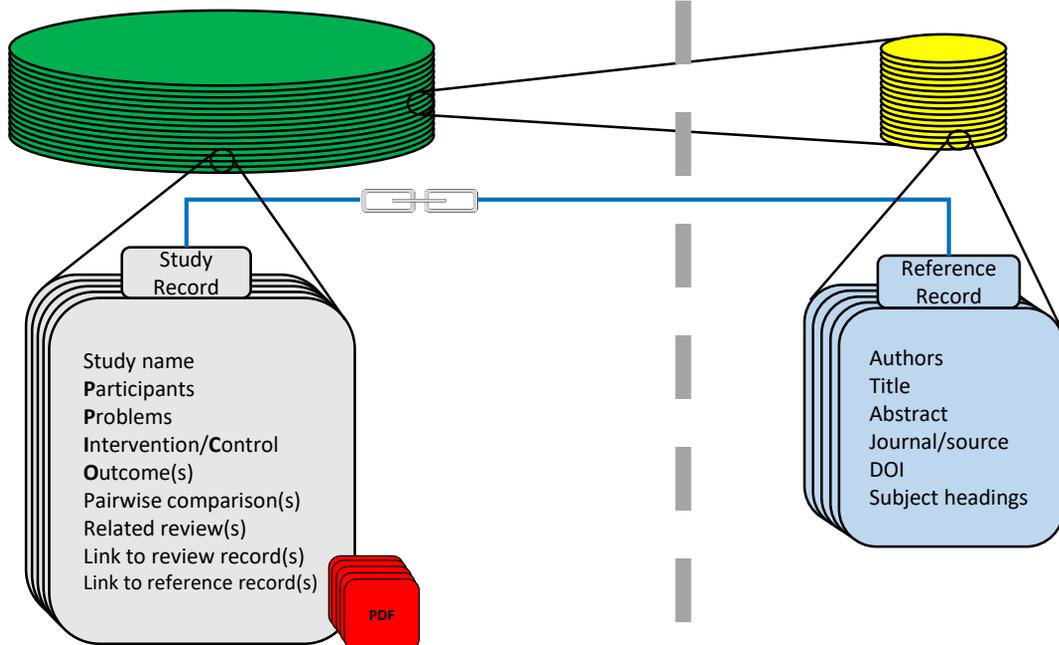
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				inhibitors		
	Diagnostic agents	6	0	Indole derivatives	5	0
	Gastrointestinal disorders (functional) drugs	7	1	Monoamine oxidase inhibitors	22	0
	General nutrients	20	0	Muscarinic receptor agonists	0	3
	Hormones - other	6	0	Neurokinin antagonists	0	3
	Hormones - sex and modulators	20	0	Neurotransmitter receptor modulators	0	3
	Hypnotics and sedatives	25	6	Nicotinic acetylcholine receptor modulators	0	11
	I.V. solution additives	8	0	NMDA receptor agonists/antagonists	0	6
	Immunosuppressants	5	0	Opioid anesthetics	8	3
	Lipid modifying agents	10	0	Phenothiazines	21	6
	Metabolites	0	2	Phosphodiesterase inhibitors	0	5
	Muscle relaxants	7	0	Serotonin receptor agonists/antagonists	10	40
	Ophthalmologicals	5	0	Sigma receptor agonists/antagonists	0	3
	Vitamins	14	0	Sympathomimetics	10	0
	Unclear	0	65	Tertiary amines	7	0
				Thioxanthene derivatives	5	0
				Unclear	0	61
	TOTALS	580	470	238	256	231

M – Marketed drug RD – Drug used only in research

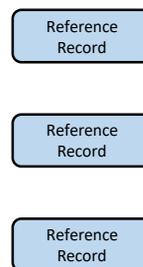
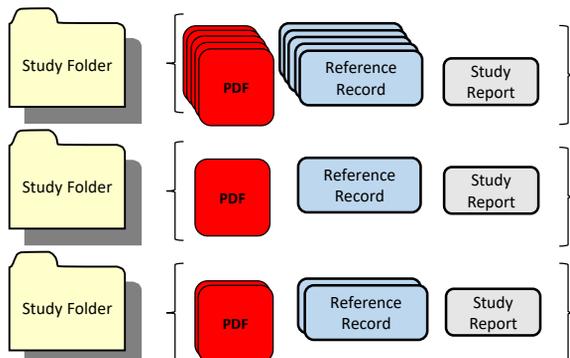
Table 6: Qualifiers of pharmacological interventions used in Cochrane Schizophrenia systematic reviews or RCTs

Qualifier Type		Example		Source	
Chemical	binder	fluphenazine enanthate	vs fluphenazine decanoate	RCT	
	duration of action	long-acting	vs short-acting		
	isomer	cis-	vs trans-		
Cost		free	vs full cost		
Delivery	injection depth	20mm	vs 50mm		
	injection site	gluteal	vs deltoid injection		
	tablet	orally disintegrating tablet	vs standard tablet		
	with meals	fasting	vs With food		
Dose	change	↓ decreasing	vs maintaining dose		Cochrane review
		↑ increasing dose	vs maintaining dose		
	oral/IM/IV	10 mg	vs 20 mg		
	plasma level titration	low	vs high		
Form	brand	brand	vs generic	RCT	
	flavour	strawberry	vs vanilla		
	size of tablet	small	vs large		
Polypharmacy	Antipsychotic	monotherapy	vs polypharmacy	Cochrane review	
	decrease	maintaining	vs decreasing numbers		
	instigate	Other drugs polypharmacy (combination)	vs treatment as usual		
Regimen	as required	as required	vs treatment as usual	RCT	
	instigation	immediate	vs delayed		
	intermittent	3 days per week	vs all week	Cochrane review	
	maintenance	continuation	vs discontinuation		
	switching	switching	vs maintaining		
	switching - method	sudden	vs tapering off		
Route		oral	vs injection	RCT	
Timing	frequency	once a day	vs twice a day		
	periodicity	three weeks	vs six weeks		
	time of day	morning	vs evening		



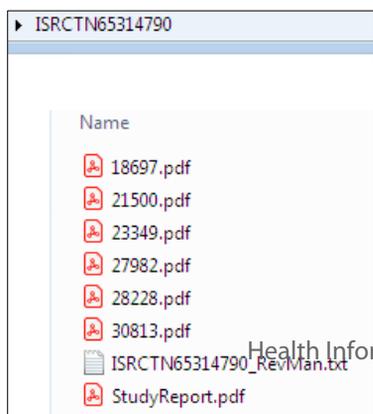
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