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Review

Long-term harms from previous use of selective serotonin reuptake inhibitors: A systematic review

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Abstract.
BACKGROUND: Millions of people are treated with antidepressants like selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). This clinical practice is based on short-term trials that have exaggerated the benefits and underestimated the harms. We also know too little about long-term harms.
AIM: To assess harms of SSRIs and SNRIs that persist after end of drug intake.
METHODS: Systematic review of placebo-controlled randomised trials of any length in patients with a psychiatric diagnosis and a follow-up of at least six months. Our primary outcomes were mortality, functional outcomes, quality of life and core psychiatric events. We searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials and checked the references for eligible articles. One researcher extracted data and another checked the data extraction.
RESULTS: Our searches returned 9,153 unique records. We included 22 papers for 12 trials on SSRIs. Median intervention and follow-up periods were 15 and 52 weeks, respectively. Median number of randomised participants was 51; only two trials had a drop-out rate below 20%.

Outcome reporting was less thorough during follow-up than for the intervention period and only two trials maintained the blind during follow-up. All authors concluded that the drugs were not beneficial in the long term.

All trials reported harms outcomes selectively or did not report any. Only two trials reported on any of our primary outcomes (school attendance and number of heavy drinking days).
CONCLUSION: The randomised trials currently available cannot be used to investigate persistent harms of antidepressants.

Keywords: SSRI, harms, long-term, antidepressants, SNRI

1. Background

The number of people treated with psychiatric drugs is increasing [1–5]. Sales of selective serotonin reuptake inhibitors (SSRIs) and similar antidepressants are estimated to be so high in Denmark, that every seventh citizen can be treated with such a drug for their entire life [6].

There are many problems with placebo controlled trials of antidepressants [6–8]. The trials are of short duration, a median of only 9 weeks [8]; withdrawal effects are almost always introduced in the placebo group because the patients were already in treatment before they were randomised; lack of effective blinding; attrition; and selective reporting of major harms [6–8]. Published papers have therefore exaggerated the benefits and underestimated the harms.

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Despite these difficulties, we do know that short term use of antidepressants can cause irritability, anxiety and panic, emotional flattening, dyskinesias [9], sexual impairment [10, 11] and also suicidality and aggression [8], even in healthy adult volunteers [12]. In observational studies, antidepressants have been linked to increased risk of dementia [13]; they may induce depressogenic effects; and the prevalence of treatment-resistant depression appears to be increasing [14]. Antidepressants have stimulant effects and rather than acknowledging this drug harm, it has led to a diagnosis of bipolar disorder in about 10% of children aged 10–14 years under the care of mental health services [15], which is a far worse disease than depression and is often treated with antipsychotics. Similar results have been reported for adults [16].

Despite the fact that we base our clinical practice on short-term trials, many patients continue on the drugs for years. A major reason for this is that they have difficulty coming off the drugs again because of withdrawal effects [17, 18], which for SSRIs are very similar to those the patients experience when they try to stop benzodiazepines [19].

Long-term use of psychiatric drugs may cause permanent brain damage, which has been most clearly documented for antipsychotics [20, 21]. Animal studies have shown that prenatal exposure to psychiatric drugs can lead to altered physiology and behaviour later in life [22, 23].

We therefore decided to do a systematic review of long-term, or persistent, harms of treatment with SSRIs or serotonin-norepinephrine reuptake inhibitors (SNRIs) after at least six months follow-up after end of a drug treatment in humans.

2. Methods

2.1. Type of studies

We included randomised, placebo-controlled trials with a parallel group design that compared antidepressant drugs with placebo. There were no language restrictions.

2.2. Participants

Participants of all ages with a psychiatric diagnosis were eligible.

2.3. Type of interventions

Trials of any length comparing SSRIs or SNRIs as monotherapy to placebo were accepted, if the follow-up period from end of drug treatment was at least six months. We also accepted trials where at least a six-month follow-up included a tapering period.

Trials allowing concomitant medication or psychosocial interventions in both groups were accepted. Wash-out periods or placebo lead-in phases were noted. We also noted to what extent drugs are administered for side effects during follow-up, as this could potentially conceal the lasting harms of the study drugs.

2.4. Primary outcomes

We extracted data at the end of follow-up. Validated scales were preferred over non-validated scales.

2.5. Our primary outcomes

1. Death.
2. Functional outcomes, e.g. job adherence, marital status, delinquency and traffic accidents.
3. Quality of life.
4. Core psychiatric events [24] – as listed in Appendix A.

2.6. Secondary outcomes

- Admission to hospital.
- Relapse/recovery rates.
- Sexual dysfunction.
- Self-rated symptom scores.
- Serious adverse events.
- Adverse events were listed under primary outcomes or serious adverse events; arbitrary thresholds for reporting were noted.
- Cognitive function, including dementia – measured on psychometric scales.

2.7. Data collection, extraction and analysis

Database searches were done in PubMed, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL) for psychiatric drugs in general (Appendix B). For additional information on harms, we looked up the included trials in www.clinicaltrials.gov and www.clinicaltrialsregister.eu.

Screening of titles and abstracts were done by one assessor (PD). When in doubt, a second observer (PG) was involved. As our data searches were very broad (see Appendix B), we lowered the number of articles to screen by including only those abstracts that contained the word 'placebo' in Endnote, and we also excluded abstracts that contained the word 'anesthesia', as trials that tested psychiatric drugs for their anesthetic properties had inadequate drug-free follow-up periods.

Possibly eligible articles were read in full by two observers independently (PD and MV) who assessed their eligibility. One observer (PD) extracted data from the articles, which were checked by another observer (PG). Any disagreements were resolved by discussion. We reviewed the reference lists of the included papers, and if necessary, we contacted the authors of the studies to obtain more information.

We assessed the risk of bias according to the Cochrane Handbook [25] and added sponsorship bias. We also included co-morbidity bias and responder selection bias, as described in the protocol for a Cochrane review on methylphenidate in adults [26].

We performed a systematic review and had planned to perform meta-analyses but this was not possible.

3. Results

Our database searches identified 9153 unique records for psychiatric drugs. After screening of titles and abstracts, 262 records remained, and after full text reading we identified 40 papers with SSRIs or SNRIs as intervention drugs regardless of the indication, 22 of which were included, as they addressed participants with a psychiatric disorder. The 22 papers represented 12 unique trials (see PRISMA flow chart in Appendix B). The median publication year for the primary publication of the trials was 2013 (range 1990 to 2016).

All trials had studied SSRIs, which were fluoxetine [27–30], fluvoxamine [31–33], sertraline [34, 35], escitalopram [36, 37] and paroxetine [38] (see Table 1 for details of the trials). For three trials the

doses were fixed [27, 32, 38], while the remaining trials titrated the dose. The trials aimed at relieving the trial participants for symptoms of depression, post-traumatic stress disorder, obsessive-compulsive disorder, panic disorder, binge eating disorder, school refusal with anxiety and benzodiazepine use in depression. Two trials were carried out in adolescents [28, 29], while the remaining trials were in adults.

The median intervention period was 15 weeks (range 7 to 32 weeks), and the median follow-up after the randomised phase was 52 weeks (range 24 to 364 weeks) for 11 trials; the remaining trial [38] accepted varying follow-up periods ranging from four to 211 weeks). Seven trials were registered in an online trial register, and two of those had registered study results [30, 35].

The median number of participants randomized to the interventions was 51 (range 31–300). The median drop-out rate was 22% (range 10% to 52%) among the 11 trials that provided numbers. The median drop-out rate at end of follow-up was 26% (range 12% to 50%) among the nine trials that provided numbers. Only two trials had a drop-out rate below 20% [33, 37]. The median percentage of male participants was 40 (range 19 to 66) for the eleven studies with information.

The tapering method was specifically described for three trials; in one, the medication was stopped abruptly [30], and two described a four-week [31] and a six-week taper [32], respectively. The remaining trials either just mentioned a taper [28, 35, 36], or did not mention it at all.

3.1. Risk of bias assessments

For sequence generation, the risk of bias was low for six trials [28, 34–38] and for allocation concealment, it was low for seven trials [28, 30, 34–38]. During the randomised phase, blinding of participants and personnel was maintained for five trials [30, 31, 34, 35, 37] and for the outcome assessors for eight trials [28, 30, 31, 33–35, 37, 38].

For blinding during the follow-up, the risk of bias amongst observers was low in two trials [30, 31], as the observers were blind to treatment conditions throughout the trial. Five trials had an unclear risk of bias, as it was not clear whether the blinding was maintained during follow-up [29, 34–37], whereas the remaining five trials had a high risk of bias because the blind was broken at the end of the intervention.

All trials reported harms outcomes selectively or did not report any. Primary outcomes as described in our methods section were only reported by two trials; one reported on school attendance [28] and the other on number of heavy drinking days [35]. For the secondary outcomes, three trials reported on remitters [27, 30, 34], and one trial reported on the self-rated Visual Analogue Scale for Depression [37].

Two trials were sponsored by both public and private grants [32, 36], one trial stated in the trial register that a medical centre in Israel was the sponsor but in the paper Lundbeck was the funder of the trial [37]. Two trials had no information on funding [29, 33]; the remaining trials were publicly funded. Three publicly funded trials disclosed conflicts of interest of the authors [30, 35, 38] who were either employed in a drug company or functioned in advisory boards or as consultants for drug companies. One trial declared no conflicts of interest but was both publicly and privately funded [36]; the remaining trials shared no information on conflicts of interest.

We assessed whether co-morbidities were allowed so that the results from the clinical trials could be extrapolated to clinical practice. The risk of bias was high for all trials, as only participants with no or little co-morbidity were included. Furthermore, all trials were biased in relation to the way the participants were recruited. No trials clearly listed the participants as being treatment-naïve and seven trials explicitly reported to have used either a placebo lead-in or a drug wash-out period before the randomisation [29–33, 35, 38]. Two trials did not exclude patients based on their previous responses to antidepressant drugs [28, 33]; two trials did not report on this [27, 36], while the remaining trials excluded patients based on their history or response to drugs, placebo or therapy.

3.2. Outcome reporting

The reporting of harms was inadequate in all the trials. Three trials had used a scale for a systematic collection of adverse events: the 36-item somatic symptom check list [34], the Fawcett scale [32], and the 58-item side effects for children and adolescents scale [28]. For the trials that predefined the use of scales, adverse events were reported for the intervention period if there were statistically significant differences between groups and no adverse events were mentioned for the follow-up [34]; adverse events were reported if they were common (difficulty falling asleep or waking up, anger outbursts, headache, irritability, lethargy, apathy, non-suicidal self-injury ideation) [28]; or adverse events were not reported at all [32]. Two additional trials provided tables of adverse events during follow-up with no mention of choice of scale: one provided a table of serious adverse events in a trial register [35], and one provided a table of seven adverse events in the paper [37]. In summary, only three trials reported adverse events collected during follow-up [28, 35, 37] and we do not know if the reporting was complete.

The reporting of outcomes for the follow-up periods was not as thorough as the reporting for the intervention periods. One study reported that fluoxetine had a positive influence on school attendance, as ten participants (50%) in the fluoxetine group had more than 80% school attendance at end of follow-up compared to four participants (25%) in the placebo group [28], but several other outcomes assessed did not show statistically significant differences between groups. Based on the findings and conclusions by the authors, all trials stated that the intervention drug had not been superior to placebo, when participants were assessed at the end of follow-up, although a few among many outcomes found the tested drug to be superior [28, 33–36].

4. Discussion

It is well known that harms caused by SSRIs can be long-lasting [18] and there are indications that they can even be permanent, e.g. for sexual disturbances [39, 40]. Withdrawal symptoms are also drug harms, and they can also persist for a long time [18].

Even though the median publication year was 2013, and even though all the trials we reviewed had a follow-up of at least 24 weeks after the randomised phase, none of them reported adequately on persisting harms of SSRIs; in fact, the reporting was very poor and selective. The authors were not even interested in reporting withdrawal effects although they likely occurred in all the trials.

Two trials reported on our pre-defined primary outcomes [28, 35]. As noted above, school attendance was higher for previously treated adolescents compared to placebo recipients [28], but given the number of trials and outcomes, this is likely a chance finding. For heavy drinking days there was no difference between drug and placebo at end of the 12-month follow-up [35]. For our secondary outcomes, data were sparsely reported for the follow-up periods and therefore useless. Thus, the outcomes that are relevant to the patients were almost universally ignored. Based on the reported effect outcomes, the SSRIs seemed to be no better than placebo at follow-up, also in the original authors' opinion. This is possibly an understatement, as the harms reporting was insufficient. In fact, it has been shown, based on clinical study reports obtained from the European drug regulators, that 12% more patients drop out during the randomized phase when they are on drug than when they are on placebo [41]. This suggests that placebo is a better pill than an antidepressant drug because the patients weigh the benefits against the harms when they decide whether to stay in a trial or to drop out.

A search on PubMed (31 May 2018) on "antidepressants AND placebo" limited to the article type "Randomized Controlled Trial" yielded 5,233 references. Thus, it seems that none of the authors of the thousands of placebo-controlled trials have been interested in finding out what the more lasting

harms are of treatment with antidepressant agents. This is very worrying, particularly considering that the patients often complain about harms long after they have come off the drugs [18, 40, 42].

Since the randomised trials are not helpful, we need to look at observational studies instead. A US national sample ($n = 15{,}365$) with a 9-year follow-up found that patients medicated for symptoms of major depressive disorder (measured on several parameters like the Instrumental Activities of Daily Living and the Composite International Interview short-form) had poorer long-term outcomes, based on symptom severity, than those who were not treated or used treatment other than medication [43]. Symptom severity could not be explained by covariates such as initial disease severity.

Another indication that long-term treatment with psychiatric drugs is unlikely to be beneficial is that, in all countries examined, the number of people on disability pension has gone up while usage of psychiatric drugs has also gone up [44]. By far the most used drug category is antidepressants.

Inadequate reporting of harms, even serious harms like deaths, is a general problem for psychiatric drug trials [6, 8, 45, 46], and the discrepancy between data in clinical study reports and in journal publications is disturbing [7, 12, 47, 48]. This means that psychiatrists are unable to choose drug treatment strategies that optimise the benefit-to-harm balance.

Compared to the above, the co-morbidity bias we found is of minor importance. The problem with representativeness of the results from clinical trials have been highlighted before, e.g. in a study that showed that only 41 of 346 (12%) outpatients would qualify for a clinical trial based on common inclusion and exclusion criteria for antidepressant efficacy trials [49].

Responder selection bias is also related to the representativeness of clinical trials. In eight of the included trials, there were problems related to this.

Conclusion

The currently available randomized trials are not helpful in elucidating what the persistent harms of antidepressants drugs are.

Conflict of interest

None to report.

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Appendix A – overview of psychiatric adverse events, as used in Bielefeldt et al., and Maund et al.

List of terms for suicidality, violence, and proposed driving mechanisms for these events
Table of terms were developed based on:

- FDA clinical review of the relationship between antidepressants and suicidality in adults
- Literature Review – Sinclair et al., Price et al. and reference checking
- Email and teleconference with Professor David Healy

Suicidality	DH comments
Core event	
Accident	
Attempt	
Burn	
Cut	
Drown	
Gas	
Gun	
Hang	
Hung	
Immolat	
Injur	
Jump	
Monoxide	
Mutil	
Overdose	
Salf damage	
Self harm	
Self inflicted	
Self injury	
Shoot	
Suici	

(Continued)

(Continued)

Suicidality	DH comments
Poison	
Asphyxiation	
Suffocation	
Firearm	

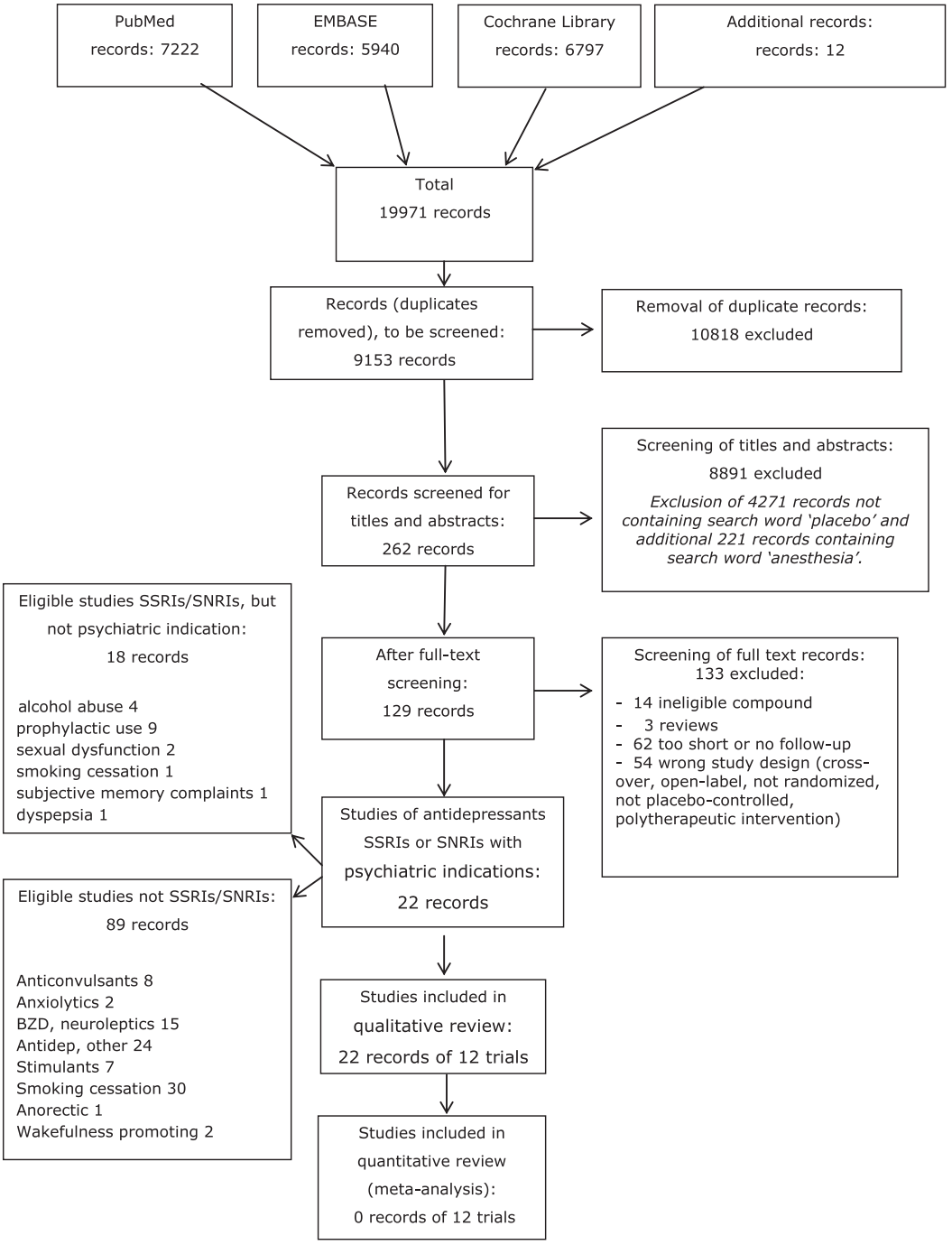
Violence	Synonyms	DH comments
Core event		
Homicide		
Physical assault	Assaultive behaviour	
Physical abuse		
Homicidal ideation		
Violence-related symptom	Criminal behaviour, Antisocial behaviour, Physically threatening behaviour	

Activation event	Synonyms	DH comments
Core event		
Jitteriness	Jittery	
Shakiness	Inner shakiness	Should be included as core event
Irritability	Increased irritability, hostility, frustration	Should be included as core event
Increased energy	Increased energy, excessive energy, unusual energy, feeling euphoric, euphoria, CNS stimulation, overstimulation, caffeine feeling, amphetamine speed like response, racing thoughts	
Mania (also listed under psychotic event)	Hypomania	Drs may use mania for both activation and psychotic events. Patients report being "manic" when they mean more active than normal i.e. experiencing activation.
Anxiety	Increased anxiety, overanxious, nervousness, anxiety attack	
Agitation	Increased agitation, aggression, hostility, argumentative	
Restless	Restlessness, motor restlessness, fidgetiness, hyperactivity, hyperkinesia, "skin crawling"	
Akathisia		
Potential event		
Insomnia	Insomnia, sleeplessness,	Not really an activation symptom
Tremor	Trembling	Should be a potential event
Panic	Panic attack, panic symptoms	
Tension	Tension increased, tenseness	
Unable to relax		
Easily startled		

Psychotic event	Synonyms	DH comments
Core event		
Hallucinations		
Paranoia		
Feelings of doom		
Delusions		
Delirium		
Psychosis		
Abnormal thinking	Intrusive thoughts, unusual thoughts, abnormal feelings	
Confusion	Disorientation, incoherent thoughts	Comment EM: "spaciness" was a verbatim term being coded as confusion in tables for SER trials but DH said verbatim term of "spaciness" should be considered emotional disturbance
Behavioural dyscontrol		
Manic reaction (also listed under activation)	Hypomania, euphoria	
Hysteria		
Potential event		
Nightmares	Bad dreams	
Abnormal dreams	Strange dreams, increased dreams, vivid dreams, intense dreams	

Emotional disturbance	Synonyms	DH comments
Core event		
Flat effect	Flattened, reduced ability to feel positive emotions, feeling blank	
Apathy	Indifference	
Anhedonic		
Disinhibition		
Depersonalised		
Derealisation	Depersonalisation	This is not an especially psychotic event and belong with emotional disturbance
Emotionally detached		
Lack of empathy		
Impulsivity		
Emotional lability		
Spaciness		

Appendix B – flow diagram and information on searches



Information on searches

For PubMed and Embase:

Filters applied: 'Randomized Controlled Trial' and 'Humans'

For indexed MeSH/Map terms, we will restrict to Major Topic (PubMed) and Focus (Embase) to include studies with main focus on the selected topic for the drug categories.

All databases:

Narrowing down to trials with follow-up we will apply the following terms: "Follow-Up Studies"[MeSH], discontinuation[tiab], maintenance[tiab], follow-up[tiab], long-term[tiab], withdrawal[tiab], extension[tiab], substance withdrawal syndrome[MeSH].

[tiab] searches in PubMed are equivalent to.mp searches in Embase and :ti,ab searches in CENTRAL. Equivalent searches were applied in the three databases.

Example, PubMed search categories, MeSH:

"Anti-Anxiety Agents" [Pharmacological Action]
"Anticonvulsants" [Pharmacological Action]
"Barbiturates"[Mesh]
"Serotonin Uptake Inhibitors" [Pharmacological Action]
"Antidepressive Agents" [Pharmacological Action]
"Monoamine Oxidase Inhibitors"[Mesh]
"Benzodiazepines"[Mesh]
"Antipsychotic Agents" [Pharmacological Action]
"Guanfacine"[MeSH]
"Clonidine"[Mesh]
"Hypnotics and Sedatives" [Pharmacological Action]
"Propylamines"[Mesh] incl atomoxetine and fluoxetine
"Central Nervous System Stimulants" [Pharmacological Action] incl. methylphenidate and guanfacine, amphetamine, lisdexamphetamine, pemoline, modafinil (tested but rejected for ADHD)
"Tranquilizing Agents"[Mesh]
+text words [tiab/.mp/:ti,ab]: SSRI, antidepressant, methylphenidate, anticonvulsant, benzodiazepine, antipsychotics

For Embase search: **explode**-function and **include all subheadings-function** was applied to include subgroups.