
Article:
Martyn-St James, M. orcid.org/0000-0002-4679-7831, Cooper, K. and Kaltenthaler, E. (2017) Methods for a rapid systematic review and meta-analysis in evaluating selective serotonin reuptake inhibitors for premature ejaculation. Evidence and Policy, 13 (3). pp. 517-538. ISSN 1744-2648

https://doi.org/10.1332/174426416X14726622176074

TITLE PAGE

Methods for a rapid systematic review and meta-analysis in evaluating selective serotonin reuptake inhibitors for premature ejaculation

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Keywords: systematic review; rapid review; rapid assessment; health technology assessment

FUNDING

This work was funded by NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC)

This report was commissioned by the NIHR HTA. The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. The final report and any errors remain the responsibility of the University of Sheffield. Eva Kaltenthaler and Matt Stevenson are guarantors.

1. Introduction

Despite the number of rapid reviews published within Health Technology Assessments (HTA) over recent years, there is no agreed and tested methodology and it is unclear how rapid reviews differ from systematic reviews (Harker and Kleijnen 2012). The use of "rapid reviews" is increasing, driven primarily by this need to engage with policy makers, healthcare professionals, and consumers in a timely manner to provide evidence-based recommendations pertaining to healthcare activities and decisions. However, while this concept of rapid review has been prominent in the discourse surrounding HTA for some time, the HTA community is yet to reach a consensus regarding their validity and the most appropriate methodology to use in their preparation (Watt et al. 2008).

Methods that limit searching by dates, databases, language and sources beyond electronic, and limiting study selection, data extraction and quality assessment to single-individual, accelerate the process, but may lead to relevant information being missed and biases being introduced (Ganann et al 2010). Restricting the scope for study inclusion, e.g., only recent studies or on studies conducted at the national level, and restricting depth of the analysis (e.g., reporting only overall findings), might also be considered to reduce steps in the review process (Abrami et al 2010). However, bias may be introduced including selection bias and publication bias. Studies might be missed by limiting the number of databases searched and reviewers involved in study selection. Additionally, rapid data extraction may miss some important information. One other approach is through a summary of existing review evidence (Chambers and Wilson 2012;Khangura et al. 2012). However, this method also relies on the quality and inclusivity of review methodology of existing reviews. Indeed, further research on this topic has been recommended in order to enhance understanding of rapid review limitations (Ganann et al 2010;National Collaborating Centre for Methods and Tools 2010).

Here we report a *de novo* method for rapid review, using a combination of randomised controlled trial (RCT) data extracted from existing reviews (without obtaining the original RCT publications), combined with a fully comprehensive systematic search to identify both RCTs potentially missed by previous reviews and RCT evidence published subsequent to existing reviews. The method was used as part of a Health Technology Assessment (HTA) short report of treatments for premature ejaculation (PE) (Cooper et al. 2015). Here we also present a case study comparing the rapid review results for one of the treatments of interest - selective serotonin reuptake inhibitors (SSRIs) - with results had a full systematic review been undertaken. This was done by obtaining the original RCT articles reported in reviews to assess the accuracy and completeness of review reporting.

In this paper we address the following research question:

How does the validity of a rapid review method in which a systematic search is run but data from RCTs identified by the search that are already reported in existing reviews are extracted from those reviews (rather than obtain each RCT publication), and data from RCTs not reported in any existing review are extracted directly from the RCT publication, compare with full systematic review methods in which all RCTs identified by the search are obtained in full and data extracted?

1.1. Aims

The aims of this study were:

1. to evaluate a rapid review method in which RCT data were extracted from existing reviews and additional RCTs not already captured by any review,
2. to assess whether this was a reliable method in terms of study identification, data completeness, data accuracy, and information on study quality and
3. to assess whether the conclusions of our rapid review would have been any different if undertaken using a traditional full systematic review data extraction method.

2. Rapid review methods

As a case study we used a rapid systematic review undertaken as part of a HTA short report (Cooper et al in 2015). The aim of the HTA short report was to systematically review the evidence base for all behavioural and pharmacological interventions in the management of PE. The review of the evidence was undertaken in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (http://www.prisma-statement.org/).

We initially ran full systematic review searches for the HTA short report that identified 102 RCTs across several interventions (behavioural, topical and systemic treatments. In addition to a narrative synthesis, we also wanted to update the evidence base by pooling data across all existing RCTs in a meta-analysis to produce contemporary effect estimates of treatment effectiveness where possible within the timescale (12 weeks). Therefore, we developed a method which involved synthesising evidence from RCTs extracted directly from existing systematic reviews, together with evidence extracted from further published RCTs. Single-arm randomised crossover design studies (participants randomised to different intervention periods) were excluded in the meta-analysis. Pooling data from participants randomised to different intervention periods as if the trial were a parallel group trial results in double-counting of participants in the analysis which constitutes a unit of analysis error (Higgins et al. 2011b). Theses and dissertations were not included. Non-English publications were

included where sufficient data could be extracted from an English-language abstract or tables. For this case study we considered evidence from one treatment option in the HTA short report – SSRIs.

2.1. Searches

Comprehensive, full systematic review searching was undertaken for the HTA short report. The following electronic databases were searched from inception to 6 August 2013 for published and unpublished research evidence: MEDLINE; Embase; Cumulative Index to Nursing and Allied Health Literature (CINAHL); The Cochrane Library including the Cochrane Systematic Reviews Database (CDSR), Cochrane Controlled Trials Register (CCRT), Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database; ISI Web of Science (WoS), including Science Citation Index, and the Conference Proceedings Citation Index-Science. Full search terms are reported elsewhere (Cooper et al 2013). The U.S. Food and Drug Administration (FDA) website and the European Medicines Agency (EMA) website were also searched. All citations were imported into Reference Manager Software and any duplicates deleted. Search filters were applied for RCTs, systematic reviews, and general reviews and guidelines.

2.2. Methodological quality assessment of existing reviews and RCTs

As part of the rapid review for the HTA short report, the methodological quality of existing systematic reviews was assessed using the AMSTAR checklist (Shea et al. 2007). The tool consists of 11 items assessing: *a priori* design; duplicate study selection and data extraction; comprehensive literature searching; the use of publication type as an inclusion criteria; reporting of included/excluded studies; reporting of characteristics of included studies; quality assessment of included studies; use of study quality in forming conclusions; methods used to combine findings of studies; assessment of publication bias; and reporting of conflict of interest (Shea et al. 2007). A quality assessment of RCTs already included in reviews was not undertaken. Methodological quality of RCTs not already captured by reviews was assessed using the Cochrane Collaboration risk of bias assessment criteria (Higgins et al. 2011a). This tool addresses specific domains, namely: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective outcome reporting.

2.3. Data extraction for rapid review

Within the rapid review for the HTA short report, outcome data from RCTs reported in reviews were extracted directly from existing reviews. For SSRIs, eleven existing reviews were identified and it was possible to check the data across these reviews for concordance (Cong et al. 2012;Huang et al. 2009;Luo et al. 2012;McCarty and Dinsmore 2012;McMahon 2012;McMahon and Porst 2011;Moreland and Makela 2005;Richardson et al. 2005;Waldinger et al. 2004a;Wang et al. 2007;Wang et al. 2010). Outcome data from RCTs not reported in reviews was extracted from the

RCT publication. One reviewer performed data extraction of each included study. All numerical data were then checked against the original article by a second reviewer.

2.4. Evaluating accuracy and completeness of rapid review method

Following completion of the rapid review for the HTA short report, a full systematic review was undertaken for one intervention (SSRIs) for this case study. All potentially relevant RCTs relating to SSRIs for PE, as identified by the HTA short report searches, were obtained in full. In order to evaluate the accuracy and completeness of the rapid review method, the original publications for all RCTs reported in existing reviews were checked against the data reported within reviews. Methodological quality of all RCTs was assessed using the Cochrane Collaboration risk of bias assessment criteria (Higgins et al 2011a). Any other quality assessment information for RCTs reported in existing reviews was extracted for comparative purposes. Relevant RCTs identified by the searches were also checked against the reviews to identify any RCTs that would have been missed had existing reviews been used as the only source of identifying RCTs up to the review's reported search date.

A summary of the comparison between the *de novo* rapid review method reported here and the full systematic review method is presented in Table 1.

Table 1: Comparison of *de novo* rapid review method with full systematic review method

Review elements	**Rapid review method used here**	**Full systematic review method**
Literature searching	Full literature search of MEDLINE and other key databases supplemented with searching of reference lists of systematic reviews and included RCTs	Full literature search of MEDLINE and other key databases supplemented with searching of reference lists of systematic reviews and included RCTs
Study selection	Two reviewers sifted searches for all relevant RCTs, identifying those already included in existing reviews	Two reviewers sifted searches for all relevant RCTs
Data extraction	Data extracted by one reviewer and numerical data checked by second reviewer of RCT data reported in existing reviews and data directly from RCT publications not in existing reviews	Data extracted by one reviewer and numerical data checked by second reviewer of all RCTs directly from original RCT publication

Review elements	Rapid review method used here	Full systematic review method
Quality assessment	Quality of existing reviews of RCT data assessed using AMSTAR Quality of RCTs within existing reviews not assessed (RCT publications reported in existing reviews were not initially obtained as beyond the scope of the HTA short report) Quality of RCTs not captured by existing reviews assessed using Cochrane risk of bias criteria	Quality of all RCTs assessed using Cochrane risk of bias criteria

3. Results

3.1. Search results

The searches for all treatments for PE for the HTA short report identified 2,283 citations. Of these, 2,181 citations were excluded, 2,174 from title and/or abstract information and seven that we were unable to obtain. A total of 41 RCTs that evaluated an SSRI against a comparator (placebo, no therapy, another SSRI, or another agent) were identified and were included in both the rapid review for the HTA short report and the full systematic review. Twenty-five of these RCTs (Atmaca et al. 2002;Atmaca et al. 2003;Biri et al. 1998;Buvat et al. 2009;Kara et al. 1996;Kaufman et al. 2009;Manasia et al. 2003;Mattos et al. 2008;McMahon 1998;McMahon et al. 2010;Mendels et al. 1995;Murat Basar et al. 1999;Panshou and Xie 2004;Pryor et al. 2006;Safarinejad and Hosseini 2006;Safarinejad 2008;Safarinejad 2006;Waldinger et al. 1994;Waldinger et al. 1997;Waldinger et al. 1998;Waldinger et al. 2001a;Waldinger et al. 2001b;Waldinger et al. 2003;Yilmaz et al. 1999;Zhou 2007) had been previously included by eleven systematic reviews (Cong et al 2012;Huang et al 2009;Luo et al 2012;McCarty & Dinsmore 2012;McMahon 2012;McMahon & Porst 2011;Moreland & Makela 2005;Richardson et al 2005;Waldinger et al 2004a;Wang et al 2007;Wang et al 2010). Data from these 25 RCTs were extracted from the systematic reviews they were reported in for the rapid review, and directly from the RCT publication obtained in full for the full systematic review.

3.2. Methodological quality of existing reviews

The search methodology and inclusion criteria for studies were varied across existing systematic reviews. The overall AMSTAR (Shea et al 2007) quality score was 1 out of 11 in four reviews (Huang et al 2009;Luo et al 2012;Richardson et al 2005;Waldinger et al 2004a), 2 out of 11 in three (McCarty & Dinsmore 2012;McMahon & Porst 2011;Wang et al 2007), 3 out of 11 in one review (Cong et al 2012), and 5 out of 11 in one (McMahon 2012). Two reviews scored 0 out of 11 (Moreland & Makela 2005;Wang et al 2007). The search methodology and inclusion criteria for studies varied across these reviews, as did the included RCTs. None of the reviews reported

independent double data extraction and only four reported an assessment of study quality (Cong et al 2012;Huang et al 2009;Luo et al 2012;Wang et al 2010). The body text of three of the reviews was in Chinese language which limited full AMSTAR assessment (assessed from English language abstract and any other English language text) (Huang et al 2009;Luo et al 2012;Wang et al 2010). Overall, the methodological quality of existing reviews was considered as being low. A summary of the reviews including the number of RCTs included and the AMSTAR quality assessment is presented in (Table 2).

Table 2. Summary of methodological quality (AMSTAR) of existing systematic reviews

Author, review type, treatments included	Treatments covered	Databases searched and dates	Additional searches undertaken by review	Included RCTs of SSRIs	AMSTAR review quality assessment	Additional RCTs identified by our searches within and subsequent to search dates of existing reviews
Cong 2012(Cong et al 2012) (China) Systematic review and meta-analysis	Fluoxetine (SSRI) *vs.* placebo	MEDLINE, EMBASE, PubMed, Ovid, CENTRAL, CBM and CNKI database July 1996 to May 2012	Google Scholar, Medical Matrix and other search engines on the Internet. Hand searching references lists (not specified which). Contact with experts in the field and corresponding authors (assume of included trials).	Five(Kara et al 1996;Mattos et al 2008;Panshou & Xie 2004;Waldinger et al 1998;Yilmaz et al 1999)	AMSTAR score, 3/11: - comprehensive literature search - study quality assessed* - publication bias assessed	*Potentially missed*: two (Ahn et al 1996;Culba et al 2008)
Huang 2009(Huang et al 2009) (China) Systematic review and meta-analysis	Any SSRI	MEDLINE, Jan 1950 to Mar 2008; EMBASE, Jan 1950 to Mar 2008; The Cochrane Library, Issue I 2008; and China National Knowledge Infrastructure (CNKI), Jan 1979 to Mar 2008	None reported	Thirteen(Atmaca et al 2002;Atmaca et al 2003;Biri et al 1998;Kara et al 1996;Mattos et al 2008;McMahon and Touma 1999;Mendels et al 1995;Panshou & Xie 2004;Safarinejad & Hosseini 2006;Safarinejad 2006;Waldinger et al 1998;Yilmaz et al 1999;Zhou 2007)	AMSTAR score, 1/11: - study quality assessed†	*Potentially missed*: four (Ahn et al 1996;Arafa & Shamloul 2006;Giammusso et al 1997;Safarinejad 2007) *Published subsequent to reported search date:* nine (Farnia et al 2009;Khelaia et al 2012;Lee et al 2012;Nada et al 2009;Nada et al 2012;Rezakhaniha & Sirosbakht 2010;Shang et al 2012;Tuncel et al 2008;Weixing et al 2012)

Author, review type, treatments included	**Treatments covered**	**Databases searched and dates**	**Additional searches undertaken by review**	**Included RCTs of SSRIs**	**AMSTAR review quality assessment**	**Additional RCTs identified by our searches within and subsequent to search dates of existing reviews**
Luo 2012(Luo et al 2012) (China) Systematic and meta-analysis	Dapoxetine (SSRI)	PubMed, BIOSIS Previews, The Cochrane Library, China National Knowledge Infrastructure (CNKI), Wangfang Database searched to 2011	None reported	Four(Buvat et al 2009;Kaufman et al 2009;McMahon et al 2010;Pryor et al 2006)	AMSTAR score, 1/11: - study quality assessed*	*Published subsequent to reported search date:* one(Lee et al 2012)
McCarty 2012(McCarty & Dinsmore 2012) (Ireland) Systematic review	Dapoxetine (SSRI)	PubMed, the Cochrane Database of Systematic Reviews, NHS Evidence, and the National Institute for Health and Clinical Excellence org.uk). To August 2011. Start date not reported	The references listed in identified articles were used as a further source of relevant studies.	Four(Buvat et al 2009;Kaufman et al 2009;McMahon et al 2010;Safarinejad 2008)	AMSTAR score, 2/11: - characteristics of included studies reported - conflict of interest statement reported	*Published subsequent to reported search date:* one(Lee et al 2012)

Author, review type, treatments included	**Treatments covered**	**Databases searched and dates**	**Additional searches undertaken by review**	**Included RCTs of SSRIs**	**AMSTAR review quality assessment**	**Additional RCTs identified by our searches within and subsequent to search dates of existing reviews**
McMahon 2011(McMahon & Porst 2011) (Australia) Systematic review	Any systemic treatment	Waldinger 2004(Waldinger et al 2004a) and PubMed from 2004 (no end date)	The references listed in identified articles were used as a further source of relevant studies.	Five(Atmaca et al 2002;Kara et al 1996;Mattos et al 2008;Waldinger et al 1998;Waldinger et al 2001a)	AMSTAR score, 2/11: - characteristics of included studies reported - conflict of interest statement reported	*Potentially missed*: eleven(Ahn et al 1996;Akgul et al 2008;Arafa & Shamloul 2006;Culba et al 2008;Farnia et al 2009;Giammusso et al 1997;Nada et al 2009;Rezakhaniha & Sirosbakht 2010;Safarinejad 2007;Tuncel et al 2008) *Published subsequent to publication date*: five(Khelaia et al 2012;Lee et al 2012;Nada et al 2012;Shang et al 2012;Weixing et al 2012)
McMahon 2012(McMahon 2012) (Australia) Systematic review	Dapoxetine (SSRI)	MEDLINE, Web of Science, PICA, EMBASE 1993 to April 2012	The proceedings of major international and regional scientific meetings.	Four(Buvat et al 2009;Kaufman et al 2009) (McMahon et al 2010;Pryor et al 2006)	AMSTAR score, 4/11: - comprehensive literature search - studies included regardless of publication type - characteristics of included studies reported - conflict of interest statement reported	*Published subsequent to reported search date:* one(Lee et al 2012)

Author, review type, treatments included	Treatments covered	Databases searched and dates	Additional searches undertaken by review	Included RCTs of SSRIs	AMSTAR review quality assessment	Additional RCTs identified by our searches within and subsequent to search dates of existing reviews
Moreland 2005(Moreland & Makela 2005) (USA) Described as a 'mini review'	Any SSRI	Not reported	None reported	Nine(Atmaca et al 2002;Biri et al 1998;Manasia et al 2003;McMahon & Touma 1999;Mendels et al 1995;Waldinger et al 1997;Waldinger et al 1998;Waldinger et al 2001a;Waldinger et al 2001b)	AMSTAR score, 0/11	*Potentially missed*: two(Ahn et al 1996;Giammusso et al 1997) *Published subsequent to reported search date:* ten(Akgul et al 2008;Arafa & Shamloul 2006;Culba et al 2008;Farnia et al 2009;Khelaia et al 2012;Lee et al 2012;Nada et al 2009;Nada et al 2012;Rezakhaniha & Sirosbakht 2010;Safarinejad 2007;Shang et al 2012;Tuncel et al 2008;Weixing et al 2012)

Author, review type, treatments included	**Treatments covered**	**Databases searched and dates**	**Additional searches undertaken by review**	**Included RCTs of SSRIs**	**AMSTAR review quality assessment**	**Additional RCTs identified by our searches within and subsequent to search dates of existing reviews**
Richardson 2005(Richardson et al 2005) (UK) Systematic review	Any systemic treatment	MEDLINE, 1966 to January 2003 and PsycINFO, 1872 to January 2003	Manuscripts were hand-searched (not clear if this was hand searching specific relevant journals) and a search of published reviews and the references of included studies	Seven(McMahon 1998;McMahon & Touma 1999;Waldinger et al 1997;Waldinger et al 1998;Waldinger et al 2001a;Waldinger et al 2001b;Yilmaz et al 1999)	AMSTAR score, 1/11: - characteristics of included studies reported	*Potentially missed*: two(Ahn et al 1996;Giammusso et al 1997) *Published subsequent to reported search date:* thirteen(Akgul et al 2008;Arafa & Shamloul 2006;Culba et al 2008;Farnia et al 2009;Khelaia et al 2012;Lee et al 2012;Nada et al 2009;Nada et al 2012;Rezakhaniha & Sirosbakht 2010;Safarinejad 2007;Shang et al 2012;Tuncel et al 2008;Weixing et al 2012)

Author, review type, treatments included	**Treatments covered**	**Databases searched and dates**	**Additional searches undertaken by review**	**Included RCTs of SSRIs**	**AMSTAR review quality assessment**	**Additional RCTs identified by our searches within and subsequent to search dates of existing reviews**
Waldinger 2004(Waldinger et al 2004a) (Netherlands) Systematic review	Any systemic or topical treatment	MEDLINE (1966–2002), Web of Science, PICA, and EMBASE (1980–2002)	The references listed in identified articles were used as a further source of relevant studies.	Thirteen(Atmaca et al 2002;Biri et al 1998;Haensel et al. 1998;Kara et al 1996;McMahon & Touma 1999;Novaretti et al. 2002;Waldinger et al 1994;Waldinger et al 1997;Waldinger et al 1998;Waldinger et al 2001a;Waldinger et al 2001b;Waldinger et al 2003;Yilmaz et al 1999)	AMSTAR score, 1/11: - characteristics of included studies reported	*Potentially missed*: two(Ahn et al 1996;Giammusso et al 1997) *Published subsequent to reported search date:* thirteen(Akgul et al 2008;Arafa & Shamloul 2006;Culba et al 2008;Farnia et al 2009;Khelaia et al 2012;Lee et al 2012;Nada et al 2009;Nada et al 2012;Rezakhaniha & Sirosbakht 2010;Safarinejad 2007;Shang et al 2012;Tuncel et al 2008;Weixing et al 2012)

Author, review type, treatments included	Treatments covered	Databases searched and dates	Additional searches undertaken by review	Included RCTs of SSRIs	AMSTAR review quality assessment	Additional RCTs identified by our searches within and subsequent to search dates of existing reviews
Wang 2007(Wang et al 2007) (China) Systematic review	Any SSRI	MEDLINE January 1 1996 to August 1 2006	None reported	Eight(Atmaca et al 2003;McMahon 1998;Murat Basar et al 1999;Safarinejad & Hosseini 2006;Waldinger et al 2001a;Waldinger et al 2001b;Waldinger et al 2003;Yilmaz et al 1999)	AMSTAR score, 0/11	*Potentially missed*: two(Ahn et al 1996;Giammusso et al 1997) *Published subsequent to reported search date:* thirteen(Akgul et al 2008;Arafa & Shamloul 2006;Culba et al 2008;Farnia et al 2009;Khelaia et al 2012;Lee et al 2012;Nada et al 2009;Nada et al 2012;Rezakhaniha & Sirosbakht 2010;Safarinejad 2007;Shang et al 2012;Tuncel et al 2008;Weixing et al 2012)
Wang 2010(Wang et al 2010) (China) Systematic and meta-analysis	Dapoxetine (SSRI)	The Cochrane Library, MEDLINE, EMBASE, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature database (CBM), Chinese Science and Technology Periodical	None reported	Five(Buvat et al 2009;Kaufman et al 2009) (Pryor et al 2006;Safarinejad 2008;Safarinejad 2006)	AMSTAR score, 2/11: - characteristics of included studies reported - study quality assessed*	*Published subsequent to reported search date:* one(Lee et al 2012)

Author, review type, treatments included	Treatments covered	Databases searched and dates	Additional searches undertaken by review	Included RCTs of SSRIs	AMSTAR review quality assessment	Additional RCTs identified by our searches within and subsequent to search dates of existing reviews
		Database (VIP) From 1979 to 2009				

AMSTAR review quality criteria: *a priori*' design, duplicate study selection and data extraction; comprehensive literature search of databases and other supplementary sources; studies included regardless of publication type; list of studies (included and excluded); characteristics of included studies reported; study quality assessed; study quality used to informed conclusions; appropriate methods used to pool data; publication bias assessed; conflict of interest statement included; *, Jadad scale (Jadad et al 1996); †, modified Cochrane Collaboration risk of bias assessment criteria(Higgins et al 2011)

3.3. Studies not included in existing reviews

Our searches identified 16 RCTs that were not included in any existing review (Ahn et al. 1996;Akgul et al. 2008;Arafa and Shamloul 2006;Culba et al. 2008;Farnia et al. 2009;Giammusso et al. 1997;Khelaia et al. 2012;Lee et al. 2012;Nada et al. 2009;Nada et al. 2012;Rezakhaniha and Sirosbakht 2010;Safarinejad & Hosseini 2006;Safarinejad 2007;Shang et al. 2012;Tuncel et al. 2008;Weixing et al. 2012). Seven of these were published subsequent to existing reviews (Khelaia et al. 2012; Nada et al. 2009;Nada et al. 2012;Rezakhaniha and Sirosbakht 2010;Safarinejad & Hosseini 2006; Shang et al. 2012; Weixing et al. 2012). However, nine RCTs (Ahn et al 1996;Akgul et al 2008;Arafa & Shamloul 2006;Culba et al 2008;Farnia et al 2009;Giammusso et al 1997;Lee et al 2012;Safarinejad 2007;Tuncel et al 2008) appeared to have been missed or excluded from existing reviews' search strategies as the publication date of the RCT was within the search dates reported by the existing reviews.

The largest number of RCTs potentially missed by a review's search strategy was eleven (Ahn et al 1996;Akgul et al 2008;Arafa & Shamloul 2006;Culba et al 2008;Farnia et al 2009;Giammusso et al 1997;Nada et al 2009;Rezakhaniha & Sirosbakht 2010;Safarinejad 2007;Tuncel et al 2008). The review concerned (McMahon & Porst 2011), which evaluated any pharmacological treatment for PE including SSRIs, reported extracting RCT data from an existing review published in 2004 (Waldinger et al 2004a), combined with electronic searches for further relevant studies published from 2004 onwards.

3.4. Summary of the number of studies in both the rapid and full systematic review

In summary: the same search was used for both the rapid review and full systematic review, the same 41 RCTS were included in both the rapid review and the full systematic review; in the rapid, review data for 25 of the 41 RCTs were extracted from existing reviews, with data from 16 RCTs not reported in any review being extracted from the RCT full-text publication; in the full systematic review, data were extracted from the full-text publication for all 41 RCTs. There were no additional RCTs included in the full systematic review that were not included in the rapid review.

3.5. Accuracy of outcome data from existing reviews

The primary outcome of interest for the HTA short report was intravaginal ejaculatory latency time (IELT). When checked across reviews, IELT outcome data was consistent and no discrepancies were evident. The most recent and comprehensive review in terms of the number of included RCTs across all SSRIs reported change from baseline values for IELT.(Huang et al 2009) Although these authors did not report how they estimated variance estimates associated with the change from baseline values used in their analysis, the mean IELT values concurred with those reported in the original RCT publications. In addition, all secondary outcome data including adverse event data reported by

reviews concurred with those reported in the original RCT publication. In summary, the error rate for RCT data extraction of IELT and secondary outcomes reported in existing reviews was low.

3.6. Completeness of outcome data from existing reviews

When checked against the RCT publication, all IELT data reported as a mean value with variance estimate were reported accurately when cross checked with existing reviews. The only additional IELT data from the original RCT publications not reported by any review were as follows: one RCT reporting IELT results classified as unsuccessful, improvement and cure, (Murat Basar et al 1999) two RCTs reporting median and range values for this outcome (Waldinger et al 1994;Waldinger et al 1997) and two RCTs (Waldinger et al 2001a;Waldinger et al 2001b) reporting p-values for the between-group difference in geometric mean without any variance estimate (Supplementary table). These data were unsuitable for pooling with IELT data (mean and standard deviation) in the meta-analysis undertaken as part of the HTA short report (Cooper et al 2013). In terms of secondary efficacy outcomes, these were in general also consistent in terms of completeness of data extraction and reporting by existing reviews (Supplementary table). The limiting factor in terms of secondary outcomes for pooling data across RCTs for the HTA short report was the varied and limited way these outcomes were assessed and reported in the original RCT publication and not the reporting in the reviews. In summary, all RCT IELT outcome data required for our analysis for the HTA short report were available from existing reviews.

Adverse event data reported by existing reviews was confirmed as accurate when compared against the original RCT publications. Additional adverse event data not included in reviews was available from eleven RCTs.(Atmaca et al 2002;Biri et al 1998;Manasia et al 2003;McMahon 1998;Mendels et al 1995;Murat Basar et al 1999;Safarinejad & Hosseini 2006;Safarinejad 2006;Waldinger et al 1994;Waldinger et al 1997;Waldinger et al 2003;Yilmaz et al 1999) However, these data tended to be greater detail regarding types of adverse events and numbers of participants (Supplementary table), and did not conflict with any conclusions regarding between-group differences in adverse events (e.g., reported p-values) presented in existing reviews. Furthermore, due to diversity of the types of adverse events these data did not facilitate any data pooling across RCTs for adverse events in the HTA short report (Cooper et al 2013).

3.7. Completeness and consistency of data on RCT quality taken from existing reviews

Only four of the eleven existing reviews (36%) reported undertaking a quality assessment (Cong et al 2012;Huang et al 2009;Luo et al 2012;Wang et al 2010). Two reviews (Cong et al 2012;Wang et al 2010) reported applying the Jadad quality scale (Jadad et al 1996) with one review reporting a quality assessment cut-off of five points or above on the Jadad quality scale to include RCTs (Cong et al 2012). Two reviews (Huang et al 2009;Wang et al 2010) applied the Cochrane Collaboration risk of

bias assessment criteria (Higgins et al 2011), however; it was unclear from the two reviews concerned how the Cochrane Collaboration risk of bias assessment criteria (Higgins et al 2011) had been converted to an overall grade. Due to the diversity of quality assessment approaches and limited number of reviews reporting a quality assessment, we considered it unfeasible make any comparisons between the quality assessments reported by existing reviews and our quality assessment of the original RCT publications for this study using the Cochrane Collaboration risk of bias assessment criteria. We did, however, undertake a Cochrane Collaboration risk of bias assessment on all 41 RCT publications obtained as full-text for the full systematic review for completeness (Supplementary table).

3.8. Comparability of rapid review findings versus full systematic review findings

The findings for the effectiveness of SSRIs in the treatment of PE, based on our HTA short report which included a meta-analysis of IELT outcomes, were that, with the exception of fluvoxamine, SSRIs are significantly more effective than placebo at increasing IELT, with the greatest increase evident for paroxetine, and that all SSRIs are associated with side effects. However, the evidence comprised RCT data extracted from existing reviews which were of low to moderate methodological quality coupled with data extracted from RCT publications not already included in a review, the majority of which were of unclear risk of bias.(Cooper et al 2013)

In terms of comparison of the two methods, the findings and conclusions arrived at from the rapid review method for safety and effectiveness of SSRIs in the treatment of PE adopted in our HTA short report, i.e., extracting RCT data from existing reviews, did not differ from those arrived at through undertaking a full systematic review extracting data directly from RCT publications. IELT data reported in existing reviews were sufficiently complete and accurate and there was therefore no difference between the findings of the rapid and the full review for the primary outcome. Of note, for the rapid review our electronic searches were run from database inception dates. Had we run our searches from the last search date reported by our included reviews, some relevant studies would have been omitted (Table 2). In terms of quality assessment, the information on study quality reported in existing reviews of SSRIs for premature ejaculation was limited across reviews and where undertaken was done so using a variety of assessment methods and we were only able to present study quality data for the 16 RCTs not included in reviews for the HTA short report which, along with the methodological quality of the existing reviews, was a limitation. As such we undertook a comprehensive risk of bias assessment of all RCTs identified for inclusion as part of the full review by obtaining the full RCT publication. The risk of bias assessment undertaken as part of the full review indicates that the majority of RCTs evaluating SSRIs for the treatment of premature ejaculation (38/41, 92.7% - supplementary table) are of unclear risk of detection bias, mainly due to

limited reporting regarding blinding of the outcome assessment. Sensitivity analyses for study quality were not planned as part of either the rapid or the full review.

4. Discussion

Within our *de novo* rapid review method reported here, we extracted RCT data reported in existing reviews of SSRIs for PE and combined these data with additional data extracted from RCTs not included in any existing review. Our searches identified additional RCTs that had been either missed by existing reviews' search strategies or inclusion criteria, or were published subsequently to the reported search dates of existing reviews. The primary and secondary efficacy outcome data extracted directly from reviews were accurate and complete when compared with the original RCT publications, with the exception of a small amount of additional data not suitable for our data pooling, and some additional information regarding type and numbers of adverse events. The findings of our rapid review for the effects of SSRIs in treating PE concurred with those that would have been reached had we undertaken a full systematic review in this area, extracting data from the original RCT publications. However, we were only able to undertake an assessment of methodological quality of all RCTs as part of the full systematic review. Reporting of study quality was limited and disparate across existing reviews.

The rapid review approach we used allowed us to synthesise an evidence base comprising one hundred two (102) RCTs across all behavioural, systemic and topical treatments for PE, forty-one (41) of which evaluated SSRIs. In addition, we were able to synthesise quantitative primary outcome data across RCTs where appropriate in a meta-analysis to produce effect estimates across all relevant RCTs. This would not have been possible had we chosen to report and summarise the results from existing reviews separately to those from fully extracted additional RCTs, as with other approaches to rapid reviews (Khangura et al 2012). We were also able to correct data synthesis errors (double counting of participants in meta-analyses) where evident in existing reviews.

Existing systematic reviews might miss studies due to limitations of their search strategies or inclusion criteria, as was evident in some of the reviews included here. The full systematic search we used as part of our rapid review method identified some RCTs apparently missed by existing reviews which, in terms of the research question, was a strength of our method. However, subgroup analyses for the effects of missing studies were outside of the scope of our HTA short report. Careful judgement should be made when employing rapid review methodology that uses existing reviews as to whether to search for additional RCT evidence subsequent to or including the search dates of existing reviews. The decision regarding an appropriate cut-off date when searching for additional studies may also depend on the completeness of the reported search strategy in existing reviews (search terms and sources searched) and the inclusion/exclusion criteria for included studies (e.g.,

using a quality assessment cut-off) and whether these factors have the potential to miss potentially important studies. In addition, decisions on whether to re-visit original RCT publications reported in reviews might be based on factors such as whether independent study selection, double data extraction and quality assessment of included studies are reported by the review or not.

The overall methodological quality (AMSTAR(Shea et al 2007)) of the existing reviews included by this assessment was low and there was limited reporting of double-data extraction or methodological quality assessment of included studies. However, we identified several reviews evaluating SSRIs in the treatment of PE that in this example of rapid reviewing helped facilitate data checking of RCT data across reviews, Whilst not all RCTs in reviews were reported by all of the reviews (owing to differences in search strategies, inclusion criteria and search dates), there was sufficient overlap (i.e., each RCT from a review was presented in two or more reviews) for cross-review data checking for accuracy. Despite the methodological limitations evident in the existing reviews, the findings for the primary efficacy outcome (IELT) from our *de novo* rapid review method reported here would not differ from those arrived at through undertaking a full systematic review extracting data directly from RCT publications. However, the limited reporting of assessment of methodological quality of include studies across reviews did not facilitate any meaningful interpretation of study quality and would not have facilitated a sensitivity analysis for study quality had this been an *a priori* defined outcome. Information on study quality could be extracted from systematic reviews in other research areas where quality assessment is better reported.

Developed from methods to conduct systematic reviews, a diverse range of rapid review methods are currently reported in the literature. A review of current methods and practice in Health Technology Assessment that compared rapid versus full systematic reviews in the areas of on the topics of drug eluting stents, lung volume reduction surgery, living donor liver transplantation and hip resurfacing reported that overall conclusions did not vary greatly in cases where both rapid and full systematic reviews were conducted (Cameron 2007). However, there is limited agreement at present regarding the contents, method and definition of a rapid review (Watt et al 2008). Furthermore, there is currently no agreed and tested methodology for rapid reviews and it is unclear how rapid reviews differ from systematic reviews (Harker & Kleijnen 2012).

The advantages of the method reported here are that we were able to: identify RCTs missed by existing review searches and any subsequently published RCTs; cross-check RCT data for consistency as there was more than one review for each RCT; undertake a double data extraction due to time saved by extracting data from existing reviews; correct data synthesis errors in existing reviews; and pool data across all RCTs to produce effect estimates and to summarise the evidence base for behavioural, systemic and topical treatments in the treatment of PE to date. Where only one

review of RCT data is available, reliability of those data cannot be checked across other reviews. In this scenario, revisiting original RCT publications might be more accurate and this decision may depend on the methodological quality and relevance of the existing review. In terms of the research question, the main limitation to the validity of the rapid review method reported here compared with a full systematic review was that we were unable to check the methodological quality of RCTs reported in existing reviews and, where reported, the quality assessment reporting in existing reviews was limited and disparate. Where methodological quality is disparate across one or more existing review, this may also necessitate obtaining the original RCT publication for a comprehensive quality assessment, especially where further RCTs not included in existing reviews are identified for inclusion.

5. Conclusions and recommendations

We evaluated a rapid review method in which RCT data were extracted from existing reviews and additional RCTs not already captured by any review, comparing it with a full systematic review method of the same topic – SSRIs for treating premature ejaculation. As part of the comparison of review methods, we evaluated whether our rapid review approach was a reliable method in terms of study identification, data completeness, data accuracy, and information on study quality in this area, compared with a full systematic review method. Searches run from database inception were used for both the rapid and the full review to identify relevant RCTs. We found in this area of research that primary outcome data available for meta-analysis (IELT) were the same whether the *de novo* rapid review method or a full review method were employed. However, due to limited reporting across reviews, quality assessment of all RCTs could only be undertaken as part of the full systematic review. Reviewers wanting to undertake a sensitivity analysis of study quality might therefore have to access all RCT publications in full to do so, should adequate data on study quality not be reported by existing reviews.

The existing systematic reviews in SSRIs for PE are of low to moderate methodological quality, the majority of which do not present an adequate quality assessment of included RCTs, which was a limitation observed by our rapid review in this area. A strength of our rapid review was that the use of full systematic review searches identified both existing systematic reviews and the RCTs included in those reviews as well as RCTs that had not been captured by the existing reviews. The limitations in reporting of study quality assessment in existing reviews that we observed might not be evident in systematic reviews in other areas and the rapid review methods reported here might therefore be useful when undertaking reviews within tight time constraints.

The circumstances under which a rapid review in which data are extracted from existing reviews without obtaining included RCT publications in full might be considered to be satisfactory in

comparison with undertaking a full systematic review are difficult to determine. Reviewers should consider both the availability and the methodological quality of existing reviews if these are going to be used as the primary source of RCT data extraction rather than obtain the RCT publication in full. If existing reviews are planned to be used, in addition to aspects of robustness of the search strategy, inclusion criteria for studies, and methods for study selection and data extraction, consideration should also be given to the adequacy of any assessment of study quality undertaken by and reported in existing reviews, especially if a sensitivity analysis by study quality is planned. These conclusions and recommendations are summarised in Table 3. Reviewers using any rapid systematic approach to conduct a review should also fully acknowledge the limitations of the rapid method used compared with full systematic review methods.

Table 3: Conclusions and recommendations

Question	Findings	Conclusions	Recommendations
Did rapid review method identify relevant studies	Some existing reviews missed potentially relevant studies Undertaking literature searches from database inception rather than search dates of exiting reviews identified these studies	Existing reviews may miss relevant studies due to limitations in literature searching, study selection methods and inclusion criteria for studies	Reviewers should consider whether to search for RCTs across all dates (as reported here) or just those published subsequent to existing review dates. This may be a balance between the time available and the methodological robustness and availability of existing reviews
Data accuracy	Outcome data in existing reviews of treatments for premature ejaculation appeared accurate when compared with the original RCT publication. The ability to cross-check data across multiple reviews in this area increased reliability.	Accuracy of data in existing reviews may be limited by robustness of data extraction process. Limited reporting of secondary outcome data (e.g., adverse events) may be evident in existing reviews.	Rapid reviewers should consider both the availability of existing reviews and their methodological and reporting quality
Data completeness	Primary outcome data across existing reviews of treatments for premature ejaculation were complete. Reporting of secondary outcome data was limited both within reviews and original RCT publications	Existing reviews may be an adequate source of primary outcome data, providing that they are of adequate methodological and reporting quality. Availability of multiple reviews may optimise availability of data.	If the rapid review aims to focus on primary outcome measures, and the availability, and methodological and reporting quality, of existing reviews are adequate, rapid reviewers could consider not obtaining the original RCT publications therein for additional data.
Information on study quality	Quality assessment and reporting of RCTs included in reviews of treatments for premature ejaculation was diverse, limited in its application, and poorly reported	Quality assessment information of RCTs included in existing reviews may be reliable if it is undertaken using an appropriate assessment method in a consistent and is clearly reported.	Rapid reviewers should consider the availability and quality of quality assessment with reviews. In some instances the original RCT publications may be required in order to undertake a standardised quality assessment across all RCTs

Question	Findings	Conclusions	Recommendations
Similarity of conclusions between rapid and full reviews	In this case, the overall findings of our rapid review concurred with those that would have been reached had we undertaken a full systematic review, extracting data from the original RCT publications	We feel that our method represents a reasonable alternative where resources for a full review are not available, and is likely to provide similar overall conclusions to a full review in most cases. The extent of similarity of conclusions using our method is likely to depend on the inclusion criteria and study quality of existing reviews	Rapid reviewers and commissioners may wish to check the availability, relevance (inclusion criteria) and methodological quality of existing reviews before deciding whether our rapid review method is likely to yield similar results to a full systematic review.

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