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REVIEW

The use of medication in selective mutism: a systematic review

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Abstract Despite limited evidence, selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs) are used to reduce symptoms of selective mutism (SM) in children unresponsive to psychosocial interventions. We review existing evidence for the efficacy of these medications, limitations of the literature, and resulting treatment considerations. Bibliographic searches were conducted in Medline, Embase, PsycInfo, Web of Science and Cochrane up to June 2015. Two reviewers independently sought studies of children with SM as primary psychiatric diagnosis, which reported response to medication treatment. Abstracts were limited to those reporting original data. Two reviewers independently assessed the ten papers reporting on >2 subjects regarding study design, key results, and limitations. Heterogeneity of designs mandated a descriptive summary. Symptomatic improvement was found for 66/79 children treated with SSRIs and 4/4 children treated with phenelzine. Only 3/10 studies had unmedicated comparison groups and only two were double-blinded. This review may be affected by publication bias, missed studies, and variability of outcome measures in included studies. Although there is some evidence for symptomatic improvement in SM with medication, especially SSRIs, it is limited by small numbers, lack of comparative trials, lack of consistent measures, and lack of consistent reporting on tolerability. The clinician must weigh this paucity of evidence against the highly debilitating nature of SM, and its adverse effects on the development of those children whose progress with psychosocial interventions is limited or very slow. Studies of optimal dosage and timing of medications in relation to psychosocial treatments are also needed.

Keywords Selective mutism · Pharmacotherapy · Selective serotonin reuptake inhibitors · Review

Introduction

Selective mutism (SM) is a debilitating disorder of childhood characterized by consistent failure to speak in certain settings, typically those outside the home [1]. Studies of its pharmacological treatment have been published since the 1990s. Since SM was recently classified as an anxiety disorder [2], it is tempting to generalize findings regarding the treatment of other anxiety disorders of childhood to this condition. For example, the Child Anxiety Multimodal Study recently concluded that children with moderate to severe anxiety disorders benefit most from a combination of serotonin-specific medication and cognitive behavioral therapy (CBT), but either treatment confers significant benefit relative to placebo [3]. One might therefore assume that these findings are also applicable to SM.

Generalizing therapeutic findings in this way, however, ignores several distinct features of SM. First, SM typically has an early age of onset relative to other anxiety disorders of childhood [4, 5], and many clinicians have limited experience medicating very young children. Therefore, medication is typically reserved for children with SM who fail psychosocial treatment. It is unclear, however, how much

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and what type of psychosocial treatment is indicated before a trial of medication. Second, children with SM often have distinct developmental risks (e.g., language impairments [6]; abnormalities of auditory processing [7]; developmental delays [8]; immigration [9]) that are uncommon in children with other anxiety disorders. These factors might affect response to treatment. Third, psychological treatments found effective in anxiety disorders of childhood (e.g., "Coping Cat" or similar cognitive behavioral programs [10]) may not be helpful in SM, or may require substantial modification [11, 12]. As psychological treatments must differ between SM and other anxiety disorders, it may not be prudent to assume that pharmacological treatment should be identical for them.

Given these differences between SM and other anxiety disorders, the decision to prescribe or not to prescribe medication to a child with SM is often left to the clinician's judgment. Medication is typically anxiety-focused (e.g., selective serotonin reuptake inhibitors or SSRIs), so when SM is assumed to be largely anxiety-related (versus related to other developmental risks) the potential benefit of medication is higher. Lack of availability of effective psychosocial interventions may also sway clinicians toward using medication in this population. Evidence-based psychological treatments for SM are often limited to specialty clinics, making them difficult to access in some areas. The most common reason that medication is considered, however, is the persistence of SM despite psychosocial interventions. When such interventions are unsuccessful or result in very slow progress, children typically fall behind their peers socially and academically. These problems often continue beyond the duration of their SM, which has a mean duration of 8 years, and predispose to high rates of psychiatric disorders in the long term [4, 5].

The desire to avoid medication in this population relates largely to a desire to avoid medication side effects. Meta-analysis shows a favorable risk–benefit ratio for SSRIs in non-OCD anxiety disorders of childhood [13], but as stated above it may not prudent to generalize such findings to SM. Moreover, young children with SM often respond to psychosocial intervention alone [12, 14]. Also, it is possible to train rural providers in such evidence-based interventions, for example by tele-health [15]. Such training may eliminate the "lack of effective alternatives" argument for medication. As reviewed below, the limited evidence for the benefit of medication in SM may be a further consideration.

To guide clinicians, a review of the evidence for using medication in SM specifically, not just childhood anxiety generally, is clearly needed. The present paper aims to provide such a review. Specifically, we present a systematic review of five relevant databases which examines the evidence for the use of pharmacotherapy in reducing symptoms of selective mutism in children suffering from this disorder. Limitations of the existing literature will be highlighted in order to suggest avenues for further research, and to suggest an approach to pharmacological treatment for children with SM of different ages until that research is done.

Method

Search strategy

No review protocol exists. To ensure a thorough review of the evidence for using medication in SM, a systematic review of five databases (Medline, Embase, PsycInfo, Web of Science and Cochrane) was conducted. Search terms were 'selective mutism' OR 'elective mutism' (an older term for the same disorder) AND drug therapy OR drug treatment OR medication(s) OR psychopharmacology OR psychopharmacologic OR psychopharmacological OR pharmacotherapy OR pharmacology OR pharmacologic OR pharmacological OR psychotropic agent(s) OR psychotropic drug(s) OR SSRI(s) OR Serotonin Reuptake Inhibitors OR fluoxetine OR sertraline OR imipramine OR citalopram OR escitalopram OR MAOI OR Monoamine Oxidase Inhibitors OR phenelzine 'medication'. The search strategies were adapted to each database. No limits were applied for language or publication date. Resulting abstracts were then limited to studies reporting original data for children with SM treated with medication. Reference lists of all included articles and reviews were hand-searched to identify additional potentially relevant articles.

Study selection

Two of the authors reviewed each study independently against inclusion criteria, and disagreements were resolved through discussions among all three authors. Inclusion criteria were children (age 0–18 years) with SM as primary psychiatric diagnosis who were treated with medication. The only exclusion criteria were studies in which SM was not the primary disorder treated (e.g., SM secondary to psychosis) or information on therapeutic response to medication was not reported.

Most were either single case reports or case reports of twins/siblings with SM. The quality of case report evidence has been questioned, particularly because it may be affected by publication bias to a greater degree than other types of studies (i.e., negative reports are rarely published) [16]. Therefore, we elected to focus on papers reporting results for >2 subjects, recognizing that these varied in methodology and even some of these were case series. Ten such papers were found, and these were examined in detail (see below). Heterogeneity of study design and outcome

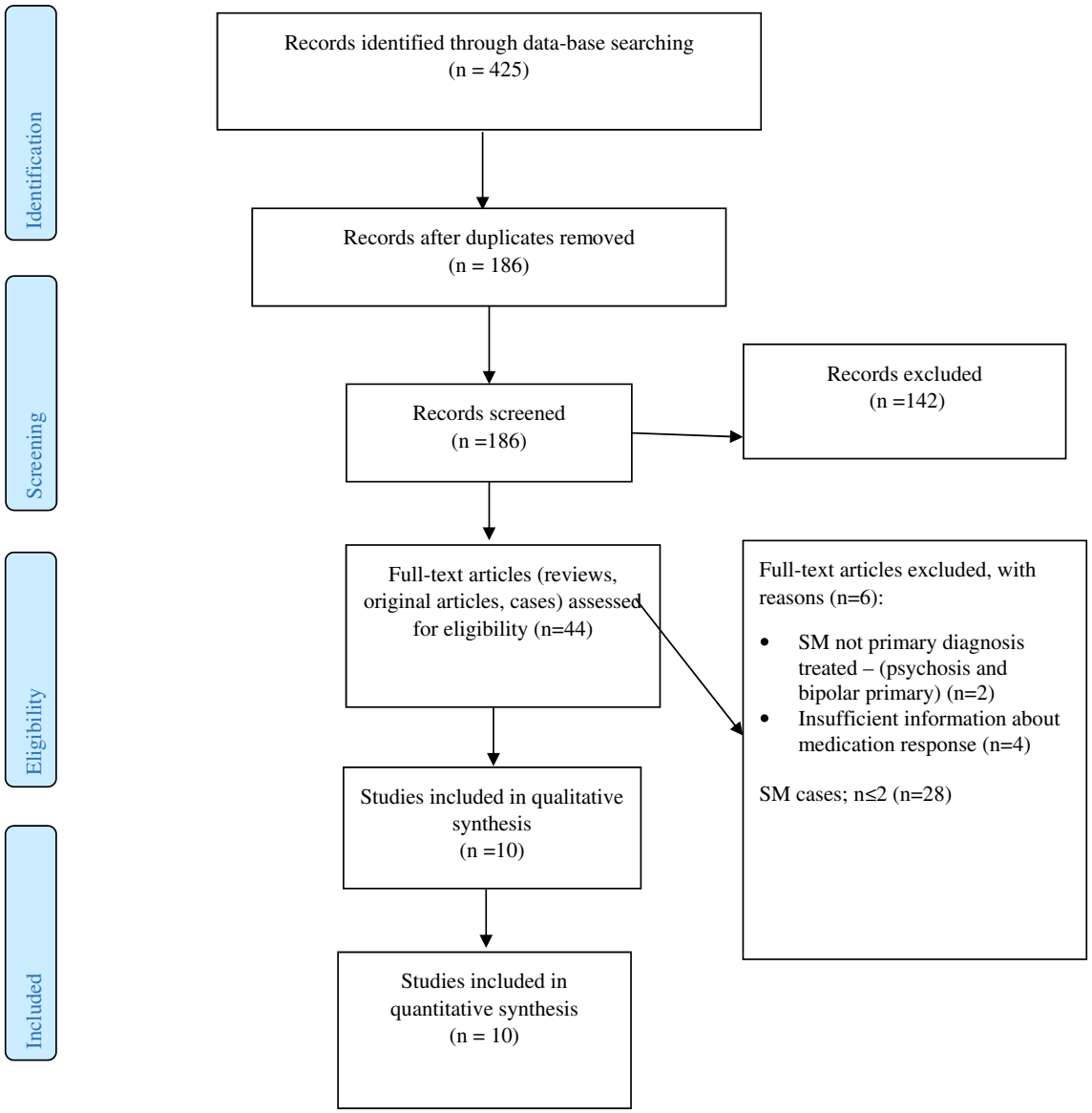

Fig. 1 Flow chart, inclusion process for the $n > 2$ studies

measures precluded the ability to perform any meta-analyses. Therefore, study characteristics are summarized and study outcomes are reported descriptively. In order to include potentially promising medications with limited evidence, 28 case studies found are also listed but not examined in detail.

Results

Figure 1 shows the flow of articles retrieved (PRISMA 2009 Flow Diagram). We found 38 abstracts reporting original data on children with SM who were treated with medication. As shown in Fig. 1, 28 studies were single case or twin reports ($n \leq 2$) and excluded from the final quantitative synthesis.

Table 1 describes the 10 studies with $n > 2$ subjects that were examined in detail. Type of medication, study design, key results, number of subjects, and main limitations are listed, and can be confirmed with the investigators if desired. Due to the paucity of evidence, all forms of symptomatic improvement (regardless of how measured) were included. Fluoxetine is the most common medication studied, though other SSRIs and phenelzine (a mono-amine oxidase inhibitor) are also represented.

Only 3/10 studies had unmedicated comparison groups [17–19], and only 2 of these were double-blinded [17, 18]. These three studies and an additional study [20] used

Table 1 Studies of pharmacological treatment of selective mutism ($n > 2$)

Study	Medication	Design	Key results	*n*	Main limitations
Black and Uhde (1994) [17]	Fluoxetine	Double-blind, placebo-controlled	All improved at 12 weeks, but still symptomatic; parent ratings of change in SM and global functioning better for fluoxetine; medication well-tolerated	15 (6 Med)	Small numbers; relatively short time interval; greater severity in the fluoxetine group; no significant findings for teacher or clinician reports
Carlson et al. (1999) [18]	Sertraline	Double-blind, multiple baseline, variable duration of medication/placebo	4/5 improved by parent report, 2/5 by teacher report when medicated; the 2 (youngest) remitted by 16 weeks; medication well-tolerated	5	Small numbers; relatively short time interval
Copur et al. (2012) [24]	Citalopram/ escitalopram	Case series	All improved by parent report with medication; medication well-tolerated	4	Small numbers; non-comparative design, lack of consistent measures
Dummit et al. (1996) [20]	Fluoxetine	Open trial	76 % (16) improved by clinician report; self- and parent measures also improved, younger improved more; medication well-tolerated in most; disinhibition in 4, of whom 2 discontinued medication	21	Short time interval (9 weeks); non-random, non-comparative design
Eke (2002) [22]	Sertraline	Randomized controlled trial, early versus late onset psychosocial treat	3/4; symptomatic improvement greater for early psychosocial treatment; details on results and tolerability not available	4	Relatively short time interval; small numbers; no unmedicated comparison group; late medication effects may have confounded psychosocial results
Golwyn and Sevlie (1999) [25]	Phenelzine	Case series	All improved over 24–60 weeks; medication well-tolerated apart from weight gain; food reaction risks	4	Non-comparative design; small numbers; lack of consistent measures
Manassis and Tannock (2008) [19]	Various SSRIs	Non-random comparison at 6 months	Greater improvement in global functioning and parent-reports of social speech with SSRIs; well-tolerated; remission in one	17 (10 Med)	Non-random (patient preferences may affect results); sampling bias (all were prior research participants)
Moreno and Pedreira (1998) [23]	Fluoxetine	Case series	All children improved in social speech; medication well-tolerated	9	Non-comparative design; combined with psychotherapy, so not clear if change attributable to fluoxetine
Schwartz et al. (2006) [26]	Various SSRIs	Retrospective parent survey	11 of 17 thought to have improved; no information regarding tolerability	17	Non-comparative design; parental recall biases
Ooi et al. (2012) [21]	Fluoxetine	Case series	Improved social speech in all fluoxetine-treated subjects, tolerability not reported	3	Non-comparative design; combined with CBT, so not clear if change attributable to fluoxetine

Med number of medicated children

Table 2 Reports of pharmacological treatment of SM by medication from the ten studies ($n > 2$ per study)

Medication	Patient numbers ($n > 2$)	Results reported in the ten studies ($n > 2$ per study)	Total numbers, including case reports ($n \leq 2$)[a]
Fluoxetine	39	Symptomatic improvement: 34/39	67 (62 improved)
Sertraline	9	Symptomatic improvement: 7/9; remission: 2/9	10 (8 improved)
Citalopram/escitalopram	4	Symptomatic improvement: 4/4	6 (6 improved)
Fluvoxamine	–	–	1 (improved)
Paroxetine	–	–	1 (improved)
Various SSRIs	27	Symptomatic improvement: 21/27, remission: 1/27	27 (21 improved)
SSRIs (total)	79	Symptomatic improvement: 66/79, remission: 3/79	112 (99 improved)
Phenelzine	4	Symptomatic improvement: 4/4	5 (5 improved)
Moclobemide	–	–	1 (improved)
MAOIs (total)	4	Symptomatic improvement: 4/4	6 (6 improved)
All medications	83	Symptomatic improvement: 70/83	118 (105 improved)

Total numbers when including case reports ($n \leq 2$) are presented in the last column

[a] All case studies reported symptomatic improvement

consistent measures and are described in more detail below; 3/10 studies combined medication and psychotherapy [21–23] and the remaining 3/10 lacked consistent measures [24–26]. All the ten studies involved SSRI medications and all reported medication was well-tolerated.

Black and Uhde [17] did a randomized controlled trial comparing outcomes for six children treated with fluoxetine and nine children treated with placebo over 12 weeks. By parent report, fluoxetine-treated children showed significantly greater improvement than placebo-treated children on the mutism change scale and global change scale based on the Clinical Global Impression scale; CGI [27, 28]. Corresponding anxiety- and shyness CGI-scales were not significantly improved. Furthermore, clinician and teacher reports did not distinguish groups. This latter result is somewhat discouraging, as children with SM are typically most symptomatic at school. However, the relatively short duration of the trial was cited as a potential limitation, and further effects might have emerged over time.

Carlson et al. [18] used a double-blind multiple baseline design to study five children using sertraline and placebo in a 16-week trial. Increased spontaneous speech with medication was observed in four children by parents and in two children by teachers. Interestingly, they noted lack of return to baseline when medication was stopped in some children suggesting that some children who initiate social speech with medication may continue to speak when it is withdrawn.

Manassis and Tannock [19] did a non-random, naturalistic follow-up of SM children who had participated in previous research after 6 months of community treatment. Ten children had been treated with various SSRIs and 7 children were unmedicated. Greater improvement was found in the medicated children using measures of global functioning from clinicians (CGAS [29]) and parents (CGI [28]), and in parent reported social speech (Selective Mutism Questionnaire; SMQ [30]). The effects of family preferences and sampling bias are significant limitations.

Dummit [20] did a 9 week open trial of fluoxetine with graduated doses in 21 children. Using the CGI, 76 % improved at end of trial, and favourable outcome was demonstrated in multiple measures, including CGAS, the parent rated Liebowitz social anxiety scale [31], and self- and parent rated social behaviour measures [32].

Table 2 shows key results by specific medication, summarized by adding reports of symptomatic improvement. Overall, symptomatic improvement was reported for 66/79 children treated with SSRIs (84 %) and 4/4 children treated with phenelzine in the ten $n > 2$ studies. Case reports ($n \leq 2$ with a total $n = 35$) were all positive for symptomatic improvement (remission difficult to judge in some cases due to variable measures), and are presented in Table 2 (last column, in italics) to show additional medications for which there is limited evidence. Fluoxetine was the most frequently used medication in case studies ($n \leq 2$), reported in 28 patients [33–52]. Citalopram was given to only two patients [53, 54]. Single case reports ($n = 1$) exist for Phenelzine [55], Fluvoxamine [56], Paroxetine [57], Moclobemide [58], and Sertraline [59]. Of note, the total number of children receiving medication reported in the literature is only about 100.

Discussion

This review highlights the paucity of evidence for the pharmacological treatment of SM, particularly the small number of well-controlled studies. As reported above, only three

of the ten larger studies ($n > 2$) reviewed had unmedicated comparison groups and only two of these were double-blinded. Small numbers, short follow-up intervals, lack of consistent measures, lack of consistent reports of tolerability, and the potential for confounding factors in some studies were other limitations. Most studies focused on SSRIs, though MAOIs were also investigated. Limitations of this review include possible publication bias in the literature and possible missed studies. However, systematic searches in multiple databases with broad key words reduced the risk of missed studies. Another important limitation is the differential study quality and the heterogeneity of improvement measures. Although we have summarized the number of patients reported to be improved, it should be noted that only 4/10 studies ($n > 2$) used consistent measures of improvement. Given this heterogeneity of measures and study quality, one could question whether our combination of the total numbers of improved patients across studies suggests a higher level of soundness than is warranted.

In part, the dearth of evidence may relate to the relative rarity of SM. School samples typically result in higher estimates of prevalence than clinical samples, but even these are usually below 1 % [60]. In rare conditions, it is difficult to collect the large number of subjects typically needed for randomized controlled trials. Collaborative studies in wide research networks would likely be needed to ensure sufficient subject numbers for such trials. Large, collaborative studies could for example, compare the benefits of medication, psychosocial intervention, and combined treatment. Alternatively, rigorous studies with small numbers of subjects can sometimes be done using multiple baseline designs where subjects serve as their own controls [61]. Carlson et al.'s study of sertraline in SM already used such a design effectively with only five subjects [18]. Such designs may also be helpful in answering questions about the optimal timing of medication in relation to psychotherapy.

For the practicing clinician, the limitations of the evidence suggest a careful risk–benefit analysis in each case. Younger children seem to respond better than older children to both CBT [14] and medication [25]. However, given the risks associated with medication, and the high rate of response to CBT (78 %) recently found in preschool children with SM [14], perhaps CBT alone should be considered 'first line' in preschool children, with medication reserved those who do not respond to a lengthy trial of CBT. In the early school years, however, CBT response is not impressive (33 % in the Oerbeck et al. trial) [14]. This finding may suggest a combined approach that includes medication in schoolchildren after a brief trial of psychosocial intervention (e.g., 3 months with limited progress evident). By easing communication in the child-therapist interaction, treatment with medication may also facilitate CBT in some cases. Due to the limited evidence available specifically on treatment of SM, and since SM recently has been categorized as an anxiety disorder, it may be useful for clinicians to lean on the literature on pharmacological treatment of anxiety disorders in general [62, 63].

Difficulty obtaining timely access to CBT may further constrain treatment decisions. Few child psychologists and child psychiatrists have specific training in CBT with children affected by SM. Therefore, lengthy waitlists for CBT sometimes result in early treatment with medication, despite a paucity of evidence for this approach.

Besides child age and CBT access, several other factors may need to be considered. Medications used in SM (both SSRIs and MAOIs) have certain attendant risks. Although potential benefit usually outweighs risk in non-OCD anxiety disorders [13], studies of risk and benefit specific to SM are sorely needed. Studies reviewed above found high tolerability, but tolerability was not consistently examined. The side effect burden and risk of interaction with other medications is typically greater for MAOIs than SSRIs [25], so SSRIs should probably be considered first. As reviewed above, there have also been more studies focusing on SSRIs than MAOIs. The consequences of not medicating a child with SM must also be considered. The risk of an often disabling long-term course [4, 5] may outweigh the risk of medication in persistent cases. However, the question of how to define 'persistent', that is how long to persevere with psychosocial interventions before considering medication, remains unanswered.

Familial and cultural views on medication must also be considered, as adherence is likely to be poor if families are uncomfortable with the child's treatment. In many countries outside the United States of America, the prescription of SSRIs for those under age 18 is either not sanctioned by health authorities (resulting in so-called "off label" prescribing) or is discouraged by local clinical practice guidelines, despite clinicians' use of such medications in children since the 1990s. Given these conditions and the paucity of well-designed medication studies in SM, clinicians may struggle to justify the use of medication to families. Until such studies are done, families must be given ample opportunity to discuss the rationale for medication, its mechanism of action (i.e., gradual anxiety reduction versus 'making the child speak'), potential risks, potential benefits, and relevant questions.

Optimal dosage and timing of medication are two further areas that have not been adequately addressed in the literature. As there is little guidance on dosage, it is usually helpful to adopt a "start low, go slow" approach in order to find the best dose. As existing trials have been relatively short-term, the optimal duration of pharmacological treatment is also unclear. Patience is important, however, as medication may reduce anxiety in a few weeks but additional time (and possibly additional behavioral intervention) may be needed before anxiety reduction results in increased social speech. It is also unclear when medication should be discontinued.

However, given the stresses associated with the start of the school year, discontinuation in the summer or in the first month of school should probably be avoided [64].

In conclusion, controlled studies of benefits and tolerability of medication in SM are clearly needed. Despite their limitations (variable study quality, heterogeneity of measures), existing studies suggest cautious optimism regarding SSRIs. While awaiting further studies, clinicians must weigh the risks and benefits case by case, and share their thoughts in a forthright manner with families as they formulate a treatment plan.

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Compliance with ethical standards

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Conflict of interest Katharina Manassis has no potential conflicts of interest apart from the financial disclosures above. Beate Oerbeck and Kristin Overgaard have no potential conflicts of interest to disclose.

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