A Systematic Review on the Pharmacological Treatment of Delusional Disorder

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Background: Pharmacological treatment is the criterion standard in delusional disorder (DD). No second-generation antipsychotic (SGA) is specifically authorized for the treatment of DD.

Aims: To evaluate the evidence available on pharmacological treatments in adults with DD and to compare first-generation antipsychotics (FGA) versus SGA.

Methods: A systematic review on pharmacological treatment of DD following the PRISMA methodology was conducted. We selected the best evidence available and analyzed it critically assessing both, biases and quality, to finally perform a narrative and quantitative synthesis.

Results: The evidence available was mainly limited to observational studies and case series. There were no randomized clinical trials. Three hundred eighty-five DD cases were included (177 of which were on SGAs). Overall, antipsychotics achieved a good response in 33.6%% of the patients. As a group, FGAs showed significant superiority compared to SGAs (good response rates were 39% vs 28%, respectively). We did not find superiority of any specific antipsychotic over another.

Conclusions: There is no strong evidence to make definite recommendations, although antipsychotics in general seem to be an effective treatment for DD with a slight superiority in favor of FGAs as compared with SGAs. Existent data are, albeit, scarce and specific clinical trials on DD, are strongly recommended.

Key Words: delusional disorder, pharmacological treatment, FGA, SGA

(*J Clin Psychopharmacol* 2016;36: 684–690)

The concept of delusional disorder (DD) has been subjected to many nosological changes throughout the history of psychiatric classification. In 1838, Esquirol made the first comprehensive description of paranoia labeling this as a partial psychosis.[1] Subsequently, Kraepelin[2] described the classical definition of paranoia as a distinct disease characterized by chronic, nonbizarre delusions that did not evolve to defective states, unlike dementia praecox (schizophrenia). However, during most of the 20th century, the term paranoia has been given a variety of meanings, including a sort of mild schizophrenia,[3,4] a disorder being part of a schizophrenia spectrum,[5] a subtype of mood disorder[6] a completely distinct entity.[7] In 1987 Diagnostic and Statistical Mannual 3rd edition revised (DSM-III-R) introduced the current concept of DD, completely similar to that of paranoia from Emil Kraepelin. Currently, DD is considered as a psychotic disorder characterized, essentially, by the presence of 1 or more delusions that persist for at least 1 month. Bizarre delusions are no longer an exclusion criterion, and there can be nonprominent hallucinations consistent with the delusional theme. Recent studies have established a population prevalence greater than previously expected for DD (0.18%).[8] The potential severity of symptoms[9] is greater than traditionally considered, as demonstrated by DD often requiring psychiatric hospitalizations.[10,11]

We considered different kind of pharmacological interventions as use of antipsychotics, antidepressants, and another kind of drugs. Drugs are the basis of the treatment of DD, namely, antipsychotics.[12] However, antidepressants, mainly SSRI, might be also useful, especially in somatic type.[13] A review addressing the impact of second-generation antipsychotics (SGAs) in the treatment of DD concluded that the degree of improvement of DD symptoms was significant regardless of the kind of antipsychotic used, that is, first-generation antipsychotics (FGAs) or SGAs. However, they reported the very poor quality of the evidence, with controlled studies lacking and evidence limited to cases studies with important methodological problems as positive bias and underreporting of negative outcomes.[14]

Traditionally, pimozide has been the drug most widely used in DD,[15] but proofs in its favor are in fact rather scarce and mostly based on 1 single small nonrandomized clinical trial in which not all patients were true cases of DD but rather a group of patients suffering from different forms of delusional parasitosis.[16] Those results were, additionally, not confirmed subsequently by another small clinical trial.[17] The rest of the evidence comes from an array of case reports.[18] Further, its possible specific mechanism of action is unknown. Pimozide appears to be an effective drug for pruritus because of its opiate antagonist properties and could be effective to treat some types of paresthesia. This therapeutic action could be explained by its dopamine blockade, by an increase in serotonergic activity[19] or by an alleged potent 5-HT2A antagonism.[20] It is plausible that such neurochemical actions can explain its efficacy in delusional parasitosis, a particular somatic type of DD. Moreover, a Cochrane systematic review on pimozide concluded that there was no evidence supporting its specific utility in DD.[21] Besides that, pimozide is no longer a first-line drug because of its known increase of QT interval and the resulting increase of cardiovascular risk.[22] Moreover, most of psychiatrists are using SGAs as a first option treatment in spite of its off-label use in DD.[13]

The official prevalence of DD is probably going to increase due to the less stringent new DSM-5 diagnostic criteria. Thus, DSM-5 new acceptance of bizarre delusions as compatible with DD diagnosis (something that excluded the diagnosis previously) is likely to render a higher prevalence of DSM-5 DD compared with DD prevalence as estimated using previous DSM, or indeed International Classification of Diseases, editions. Such plausible increment would happen at the expense of cases that earlier would have been diagnosed as schizophrenia merely on the basis that delusional content was bizarre. Very recently, a Cochrane systematic review on the treatment of DD has been published.[23] They only found a randomized clinical trial exploring the effects of 2 different psychotherapies, that is, CBT treatment versus supportive psychotherapy. No randomized clinical trials using psychotropic drugs were found at all. However, as we mentioned before, the standard empirical and clinical treatment for DD is pharmacological and, although evidence on the use of psychotropic drugs in DD is very limited, it is needed to have a clearer insight into their effects in DD and to review systematically what we know to gain the best available information to identify the best candidates that could be tested in future clinical trials.

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Received January 28, 2016; accepted after revision August 2, 2016.
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ISSN: 0271-0749
DOI: 10.1097/JCP.0000000000000595

MATERIAL AND METHODS

Criteria for Considering Studies for This Review

A wide array of published studies, in multiple languages, ranging from randomized clinical trials to observational studies, on the pharmacological treatment of DD was screened. Single case reports were excluded. Participants were adults fulfilling DSM-5 diagnostic criteria for DD and subjected to psychotropic drug therapies for its treatment. The primary outcome measured was the remission rate of psychotic symptoms with respect to baseline scoring as determined by the use of clinical scales validated to measure psychotic symptoms or, in their absence, by clinical records. We summarized all outcome information into 2 broad categories of response: "full remission" or "marked improvement" if there had been a symptom improvement of 50% or more and "Poor response or partial response" when such improvement was lower than 50%. As secondary outcomes, we took into account adverse effects and adherence when available.

Search Methods for Identification of Studies

A thorough electronic search in multiple languages using PUBMED and Web of Knowledge was carried out. The terms "paranoia" or "delusional disorder" and "treatment" in title and/or abstract were used as search strategy. We searched data published until November 2015. In addition, to check the existence of ongoing clinical trials, we looked for it in 2 websites: Clinical Trials (https://clinicaltrials.gov) and Current Control Trials (http://www.controlledtrials.com). We also searched using other resources, such as references lists included published papers and even bibliography referenced in available textbooks on DD. When data were incomplete, we tried to contact to the authors to complete those.

Data Collection and Analysis

Two different authors performed independent searches of citations and paper selection. They inspected all different abstracts before selecting them for the systematic review, and then compared the abstracts with those obtained by one another. When disputes arose about studies to include in the review, the full article was evaluated and subsequently a discussion between the authors was held to reach a consensus agreement. In the event, we included only those studies reporting type of drugs used reporting both, dosage and treatment outcome. After this, 2 different collaborators extracted and compared the data from tables, text, and figures. If disagreement, a discussion between authors was held to solve it. Data were then transferred on to an electronic data form compatible with software for statistical analyses. Thus, we included symptom-scoring changes from baseline to endpoint if such data were available. Because data proceeded from a variety of validated clinical scales or from clinical records, we decided to convert such information into 2 categories, good response (at least 50% reduction in baseline scale) or poor response (less than 50% reduction), an approached used elsewhere.[24] In many occasions, we did not have scale scores but just clinical records of improvement recorded as "full remission," "marked improvement," "nonresponse," or the like. In such case, we did our best to also fit such clinical responses onto 1 of our 2 broader response categories mentioned earlier. We chose just 2 response categories as outcome, instead of more informative outcomes split into 3 categories or more, given that most studies only provided 2 categories.

Assessment of Risk of Bias in Included Studies and Quality of Body of Evidence

To evaluate the risk of bias, the criteria established in the Cochrane Collaboration tool[25] were used. These criteria analyze the risk of bias in 5 domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting, and other source of bias. Risk of bias was, hence, evaluated by comparing and analyzing different results across the different studies. The Grading of Recommendations Assessment, Development and Evaluation system[26] was used to rate the quality of the body of evidence, according to methodological quality, directness of evidence, heterogeneity, precision of effect estimate and publication bias. Such system allows study classification into high, moderate, low, and very low quality of evidence. When disagreement between researchers appeared, it was solved through discussion between them.

Measures of Treatment Effect

The data from the different studies included was pooled and the proportion of good response (≥50%) for every drug treatment was estimated. Then, we used a 2×2 table to calculate χ^2s and relative risks to compare the effectiveness of the different treatments. For this purpose, the Epi-Info 7 statistical package (CDC, Atlanta, GA) was used. Epi-Info is a World Health Organization–supported public domain software package designed for the global public health community of practitioners and researchers developed by the Centre for Disease Control and Prevention. It provides a free statistical program with epidemiologic statistics, graphs, and maps (https://wwwn.cdc.gov/epiinfo/html/downloads.htm).

Data Synthesis

It was not possible to perform meta-analysis due to the large clinical and methodological heterogeneity of the different studies found. Thus, instead of this, we proceeded to aggregate the data for every drug as abovementioned, calculated rates of good response and compared them. For this reason, we wrote a narrative review and built tables for the aggregated data and for the studies that were finally included.

RESULTS

Results of the Electronic Search

A total of 1295 studies were found and screened, 526 in PUBMED and 769 in WOK. Duplicates were eliminated, and finally, 1061 were obtained. Subsequently, a total of 53 full-text articles after title/abstract screen were retrieved for further scrutiny. Most of these articles were written in English but we also included those found in Spanish, Danish, and German. After full text screen, 19 articles were excluded due to lacking of inclusion criteria, and another 8 articles were also excluded during the data extraction process because of missing data or impossibility for data extraction. Thus, finally we were able to include 26 articles[13,16,17,27–48] in this review (Fig. 1).

We found a high degree of clinical heterogeneity among studies including a wide range of treatments, response rates, and response criteria. Thus, for olanzapine, the range of good response was between and 0%[28] and 66%[31]; for pimozide, between 0%[17] and 90.9%,[36] and for risperidone, between 28.5%[29] and 100%,[31] respectively. Newest studies[13,28–30] tended to show a lower response rate (18.2%–24.4%) than older ones (57.9%–90.9%).[36,42,44] The latter used FGAs, mainly pimozide, and most of them focused on the somatic type of DD (nearly always delusional parasitosis). Newer studies include predominantly persecutory type DD cases,

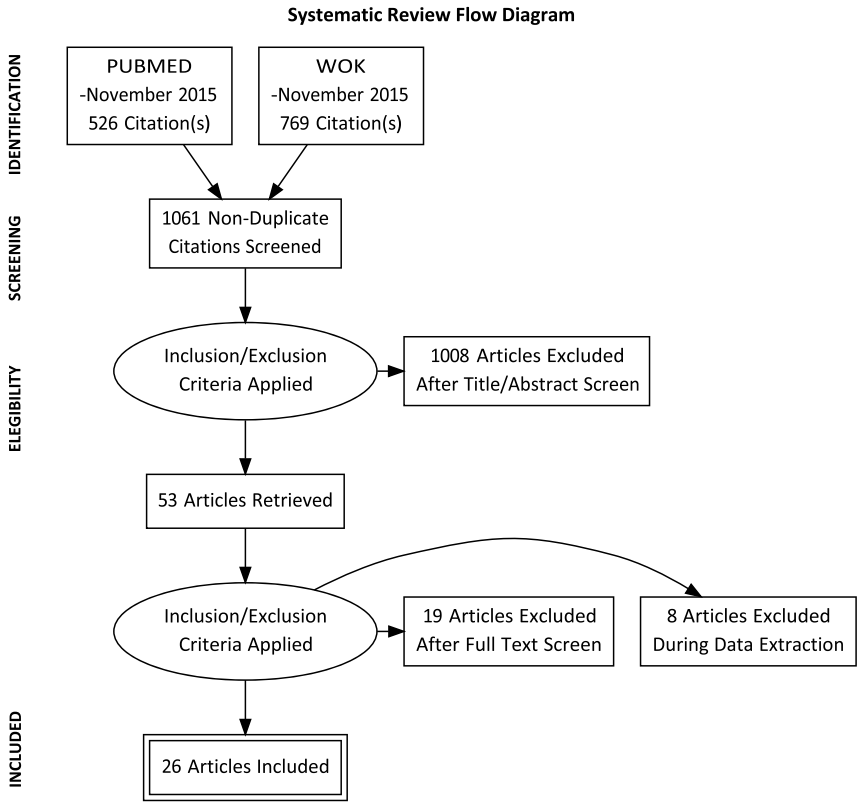

FIGURE 1. Systematic review flow diagram.

with the exception of that of Kenchaiah et al[29] and tend to report patients treated with SGAs. There were no randomized clinical trials. Most of the studies were observational or case series with a considerable degree of bias or other methodological limitations. The most important studies are displayed in Table 1.

Absence of Randomized Clinical Trials

Only 2 small experimental trials were found, showing high risk of bias, both of them using pimozide. The first study[36] paved the way for the use of pimozide in DD. It was a nonrandomized double-blind cross-over trial with 11 patients, a 90.9% of patients improved markedly. However, the small sample and the high risk of bias did not permit established robust recommendations. Another small nonrandomized quasi-experimental study with 7 patients enrolled[17] and evaluated with brief psychiatric rating scale failed to find statistical differences between pimozide and placebo. Therefore, based on these studies, it was not possible to make strong recommendations for pimozide, due to high risk of bias and methodological limitations.

Observational and Case Series Studies

A small group of case series studies were found, all of them with a high risk of bias although the difficulty of conducting studies in a low-prevalence disorder should be taken into account (Table 1).

A quasi-experimental study provided interesting but short information, being only published as abstract.[49] It reported that patients were randomly assigned to 3 treatments groups: haloperidol (n = 41, 5–20 mg/d), risperidone (n = 49, 2–6 mg/d), and olanzapine (n = 45, 10–20 mg/d), and subsequently, they were evaluated with the positive and negative symptoms scale (PANSS) and the Clinical Global Impression scales before and after 6 months of treatment. It was not specified how the randomization was carried out. At baseline, there were nonstatistically significant differences among treatment groups regarding PANSS and/or Clinical Global Impression scores. At the endpoint, there were statistically significant differences ($P \leq 0.001$) between groups in baseline PANSS scoring reduction favoring risperidone (22.2% patients showing >50% of reduction in PANSS baseline; 10 of 45) and olanzapine (24.4% patients showing >50% of reduction in PANSS baseline; 10 out of 41) versus haloperidol (9.4% patients >50% of reduction in PANSS baseline; 3 out of 32). Moreover, those were better tolerated than haloperidol.

The case series study providing more complete information was performed in India in 2007.[28] They used the information contained in clinical files records. It reported information about 88 cases of DD. 18.2% of the patients showed good response (≥50% improvement) to antipsychotics, and the 42% of them partial response (<50% improvement). Risperidone showing 35% good response was the most effective treatment.

Another observational study from Spain[33] provided 45 patients treated with SGA. They compared 2 groups composed by 29 patients treated with SGA and 16 with risperidone long acting injection (LAI) and paliperidone palmitate. At 6 months follow-up, patients treated with LAI showed lower scores in the PANSS-negative subscale when compared with patients treated with oral antipsychotics (12.129 [1.234] vs 16.324 [1.255]; $P = 0.027$).

The need of an adequate duration of treatment was emphasized by 1 observational study carried out in a prison in the United States.[31] The most remarkable fact was that 10 of 17 patients needed to be treated at least 3 months to restore patients' global capacity. Haloperidol decanoate (25–150 mg/28 days) showing good response in 69% (8 of 13) and risperidone

TABLE 1. Main Included Studies

Study	Type of Study	Sample Description	Core Outcomes	Adverse Effects and Adherence
González Rodríguez et al, 2014[33]	Observational.	N = 45 with oral and LAI SGA. 82.2% women. 52.40 (11.76) 80% persecutory type	Higher reduction of PANSS negative subscale in LAI group ($P = 0.027$).	Good adherence, 66%
Zivkovic et al, 2011[30]	Observational.	N = 135. 100% men. Haloperidol group age 41.6 (5.3); risperidone group age 42.1 (5.6); olanzapine group age 41.7 (5.1)	Risperidone and olanzapine higher reduction of baseline PANSS scoring than haloperidol ($P \leq 0.001$)	Percentage of adverse effects (extrapyramidal side effects) which requested additional therapy were significantly lower in risperidone 22.22% (10 patients) and olanzapine 19.51% (8 patients) than in haloperidol 56.25% (18 patients) group.
Kenchaiah et al, 2010[29]	Case series	N = 20. Age of onset 49.7 (19.3). Somatic type.	Better response with risperidone (28% good response; 4 of 14) than other SGA.	
Grover et al, 2007[28]	Observational retrospective of clinical files.	N = 88. 55.7% women. Age 41.8 (15.2)	18.2% good response and 42% partial response to antipsychotics. Better response with risperidone. 7 of 20.	25% of side effects. Better adherence with pimozide.
Herbel et al, 2007[31]	Observational retrospective study of clinical files.	22 men with DD imprisoned submitted to compulsory treatment. Most persecutory type.	10 of 17 responder patients needed to be treated at least 3 months. 75% restored competency. Haloperidol decanoate, good response in a 69% (8 of 13).	FGA and SGA were well tolerated.
Silva et al, 1998[17]	Non-randomized quasi experimental study.	N = 7. Age 29–60 y. 85% women. 5 persecutory type.	Pimozide doses 4.6 ± 1.2. Range, 2–12 mg/d. No differences between pimozide and placebo.	Good compliance.
Srinivasan et al, 1994[27]	Cases series	N = Men: 7; Age: 47 y. Women 12; Age, 6.4 y. Somatic type.	57.9% full recovery. 11 of 19. Full remission maintained more than 6 mo in 7 patients.	
Ungvari, 1984[44]	Cases series	N = 19. 6 men. Age, 66.1 y. Somatic type.	Pimozide (2–5 mg/d): 66.7% good response (full remission)	
Hamann et al, 1982[36]	Non-randomized double blind crossover trial	N = 10. 100% women. Somatic type. Mean age, 65.6 y. Somatic type.	Pimozide (1–5 mg/d) better than placebo ($P \leq 0.012$)	Side effects with pimozide 8 out of 11 versus 5 of 9 with placebo.
Frithz, 1979[42]	Cases series	N = 15. 100% women. Age, 62.4 y. Somatic type	Fluphenazine (7.5–12.5 mg/mo): 70% good response (7 of 10, full remission) Flupenthixol depot (6–20 mg/mo): 80% good response (4 of 5 full remission)	50% of extrapyramidal effects, relieved with anticholinergics.

(2–4 mg/d) showing 100% good response (3 of 3) were the most effective treatments.

Additionally, there are a group of studies with somatic DD patients, mainly delusional infestation.[16,27,29,34,39–42,46–48,50] Most of these studies are very old and used FGAs, mainly pimozide, as first-line treatment. The overall good-response percentage was higher than 60% (Table 1).

FGA Compared With SGA in the Treatment of DD

We included a total of 385 cases, 198 using FGAs, 177 on SGAs and 10 cases on antidepressants (Table 2). Antipsychotics in general achieved good response in just over a third (33.6%) of treated patients. Moreover, when compared, SGAs (good-response rate = 27.7%) were significantly inferior to FGAs (good response rate, 38.9%; relative risk (RR), 1.40; 95% conficence interval (95% CI), 1.04–1.88; χ^2, 5.2595; $P \leq 0.02$). Pimozide, showing good response in 38.7% of cases, was not superior or different to the rest of FGA antipsychotics that showed 39% of good response (χ^2, 0.0024; $P \leq 0.96$; RR, 0.99; 95% CI, 0.69–1.40). Risperidone, showing 33% good response, was also not superior to other SGAs that exhibited good response in 22% of cases (χ^2, 2.6115; $P \leq 0.10$; RR, 1.49; 95% CI, 0.91–2.44). Finally, there was an anecdotic sample (n = 10) of DD patients, mostly somatic type, treated with antidepressants[13,29,37] showing a good response rate of 50%.

DISCUSSION

Quality of the Body of Evidence and Limitations

When using the very strict Grading of Recommendations Assessment, Development and Evaluation system to classify evidence

TABLE 2. Treatment Effectiveness

Treatment	Good Response (≥50%)	Poor or Mild Response (≤50%)	n = 385	Statistical Analysis
Risperidone (0.5–6 mg)	30 (33%)	61 (67%)	91	Risperidone vs other, SGA; χ^2, 2.6115; $P \leq 0.10$; RR, 1.49; 95% CI, 0.91–2.44
Olanzapine (10–20 mg)	13 (20.6%)	50 (79.4%)	63	
Other SGA: quetiapine (25–700 mg), clozapine (25–500 mg), amisulpride (100–400 mg), paliperidone (6–9 mg), aripiprazole and ziprasidone	6 (26.1%)	17 (73.9%)	23	
Pimozide (1–12 mg)	36 (38.7%)	57 (61.3%)	93	Pimozide vs other FGA; χ^2, 0.0024; $P \leq 0.96$; RR, 0.99; 95% CI, 0.69–1.40
Haloperidol (1–20 mg/d, 25–150 mg/28 d)	16 (29.6%)	38 (70.4%)	54	
Other FGA (fluphenazine 12,5–25 mg/14 d; perphenazine, 16–40 mg; chlorpromazine, 150–300 mg; trifuoperazine, 10–15 mg; perithiazine, 5 mg/d)	25 (49%)	26 (51%)	51	
FGA	77 (38.9%)	121 (61.1%)	198	FGA vs SGA $\chi^2 = 5.2595$; $P \leq 0.02$, RR, 1.40; 95% CI, (1.04–1.88)
SGA	49 (27.7%)	128 (72.3%)	177	
Antipsychotics	126 (33.6%)	249 (66.4%)		
Antidepressants (paroxetine, 60 mg; sertraline, fluoxetine, 20 mg; clomipramine, 60–120 mg)	5 (50%)	5 (50%)	10	

quality, evidence on this topic should be considered of a "very low" degree, because there are virtually no clinical trials on DD. However, in real terms, such qualification is not entirely fair if we consider that DD is both relatively low prevalent and generally underresearched. Hence, in the light of current knowledge, this study should be considered as portraying the best existing evidence and, consequently, as one providing the best available conclusions. Certainly, not only could we not find randomized clinical trials reporting information on effectiveness in DD but, also, many studies did not report complete information on aspects, such as sociodemographic characteristics, adverse effects, comorbidity, or adherence. Quite often, many studies did not measure the effect using clinical scales as outcome measures but, rather, just registered response on clinical records. Two of the larger studies[28,31] were based on retrospective records in clinical files implying a risk of bias in how outcomes were evaluated.

Evidence on pimozide use was also quite poor. Thus, the main study using pimozide, on which early pimozide use was based,[36] was nonrandomized and used a very small sample. All cases were somatic type and had important comorbidity. They did not report how blinding was performed. Additionally, later studies[17] did not replicate previous results on pimozide.

There were also very few studies reporting results using SGAs, and all of them were observational studies or case series. Yet, we report here the largest number of cases published up to date.

Finally, only a few studies provide data on parenteral administration. The most interesting one comparing oral SGAs with LAIs showed a moderately higher effectiveness in favor of LAIs on negative symptoms only.[33] However, its comparative design did not allow drawing any definite conclusions.

MAIN FINDINGS

To date, this is the review including a larger number of patients on SGAs (n = 177) if compared with the first one by Munro and Mok[51] (that used only patients on FGAs, mainly pimozide, n = 143), or a more recent one by Manschreck and Khan[14] including just 33 cases using SGAs. Overall, antipsychotics accomplished a good response in 33.6% of cases. Moreover, FGAs were significantly more effective than SGAs. This result contrasts with that of previous reviews reporting good response regardless the antipsychotic type used.[14] Besides, pimozide, traditionally considered the standard treatment for DD, did not attain the best outcomes. Parallelly, pimozide is no longer a first-line treatment in psychosis due to its high risk for increasing the QT interval and cardiovascular risk.[22] Antipsychotics appear to be useful in the control of the symptoms of DD, although the percentage of good response is clearly lower than that reported by previous studies. It is also worth emphasizing that response is likely dependent on an optimum length of treatment, reported as at least 3 months.[31] Plausibly, our definition of good response is also more exigent than in previous studies and partial and poor responses are grouped, what might have contributed to underestimate good response.

In the first review by Munro and Mok[51] recovery was achieved in 52.6% and partial recovery in 28.2% of included DD cases. In the Manschreck's review,[14] reported response rate was quite similar, that is, 49.3% and 40.3%, respectively. According to another systematic review, primary delusional infestation, a type of somatic DD, responded to antipsychotic treatment in a range of 60% to 100%.[52] We need to emphasize that in the newest studies[13,28–30] providing a higher number of cases, the effectiveness of antipsychotics in DD has been, on the whole, lower than that reported in older studies.[36,42,44] Thus, the latter studies incorporated a higher number of DD patients of persecutory type and also tend to include more cases treated with SGAs than older studies where FGAs and DD somatic type are overrepresented.

Such response rate discrepancies may be due to a variety of reasons. First, DD somatic type might respond better than other types. Thus, Manschreck's review[14] found that patients with somatic type treated with pimozide responded better than those with other DD subtypes, whereas Munro's review[51] assessing 143 cases with pimozide, 129 of them somatic type, did not conclude any better response rate by DD subtype. Second, there might well be an influence of publication bias that might also have varied across time, because it is increasingly more difficult to publish reports using nonobjective outcomes measures that were more acceptable when FGAs were the only treatment option. Third, there is great methodological heterogeneity what, in turn, can bias summarizing outcomes (nearly all studies are case series report and many of them, especially the oldest ones, did not use objective, clinical-scale outcome measures). Fourth, there might exist a genuine higher efficacy of FGAs compared with SGAs.

However, we have not considered outcomes measures, such as adherence or tolerability that traditionally have been reported as more favorable in SGAs than FGAs.[53] It is plausible that if those outcomes were included in our analysis, overall utility of SGAs in DD was better than that just looking at response.

The role of the antidepressants (SSRI and TCAs) in clinical practice needs to be investigated thoroughly. At this moment in time, only a few case reports have been published. Nonetheless, it is noteworthy that, overall, response rate to antidepressants was the highest among all drug types included (50%), even superior to that found when using antipsychotics (well under 40%). Interestingly, some authors have underlined a possible involvement of a serotonergic dysfunction in the pathogenesis of DD.[19,20,54] It has also been posed that this relatively good response to antidepressants could be due to a particular effect on somatic DD type, because some cases of somatic DD type could be mistaken with obsessive-compulsive disorders with either delusional beliefs or a poor insight.[54] Although our findings are based on very few cases (n = 10), should future studies confirm that antidepressants were indeed useful in DD treatment, this could open an interesting pathway to a better treatment, possibly in combination with antipsychotics and/or psychotherapy. Indeed, antidepressants tend to have less severe side effects than antipsychotics and therefore the benefit-risk balance could plausibly be also favorable to antidepressants.[54] On the other hand, response to antidepressants maybe based on its efficacy over depressive symptoms in DD which have also been recently reported as part of DD itself and conceptualized as its depressive dimension.[55] Moreover, we pose that specifically tackling all symptom dimensions described within DD can be a useful alternative approach helping to improve a holistic treatment plan for DD patients. Additionally, consideration should be given to the therapeutic potential of other drugs that can have plausible utility in negative or cognitive symptom dimensions described in DD, such as N-methyl-D-aspartate (NMDA)[56,57] or gamma amyno butyric acid (GABA) agents.[58]

CONCLUSIONS

Current evidence is mostly limited to observational studies and case series, and we suggest the need of future specific clinical trials on DD treatment to reach more solid conclusions. Antipsychotics are likely moderately effective and possibly the best pharmacological option in the treatment of DD even when antidepressants might be a potential alternative or a treatment booster. We found a mild superiority in favor of FGAs compared with SGAs in terms of effectiveness although we did not have enough data to take tolerability into account.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflict of interests. This review did not receive any source of funding.

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