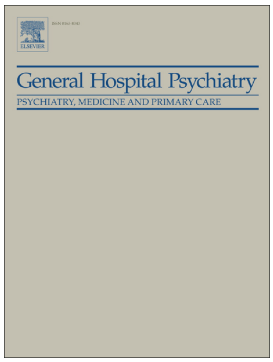

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ARIPIPRAZOLE FOR THE TREATMENT OF DELUSIONAL DISORDERS: A SYSTEMATIC REVIEW

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ABSTRACT (197 words)

Background: Delusional disorder is an uncommon psychotic disorder. The first-line treatments for this chronic and resistant condition are antipsychotic medications, usually associated with several side effects that can exacerbate poor adherence. Conversely, aripiprazole is a well-tolerated antipsychotic drug that is effective in the treatment of other psychotic disorders.

Here, we aimed to systematically review and summarize the currently available literature to evaluate the effectiveness and tolerability of aripiprazole in delusional disorders.

Methods: A comprehensive literature search from inception until February 2020 was performed in PubMed, Cochrane Database of Systematic Reviews, and Scopus databases using The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Results: We identified 21 single cases of delusional disorders, mostly somatic type, treated with aripiprazole. All studies reported patient clinical improvements after the beginning of the treatment with aripiprazole. The average dose of aripiprazole was 11.1 mg/day, and the average time to achieve a clinical response was 5.7 weeks. Few adverse effects were reported, including asthenia, extrapyramidal symptoms, hyperprolactinemia, and insomnia.

Conclusions: Our findings suggest that aripiprazole may be an effective treatment for delusional disorders with good tolerability. Further studies comparing aripiprazole with other antipsychotics in the treatment of delusional disorders are needed.

Keywords: delusional disorders, aripiprazole, effectiveness, tolerability, systematic review

INTRODUCTION

Delusional disorder (DD) is a relatively rare psychotic disorder characterized by prominent delusions in the absence of other mood or psychotic symptoms.[1][2]

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), DD is associated with the presence of one or more delusions that persist for at least 1 month, not explained by another physiological, substance-induced, medical or any other mental condition. Bizarre delusions are no longer an exclusion criterion and non-prominent hallucinations consistent with the delusional theme can be present. [3] Several psychotic disorders, including schizophrenia, psychotic mood disorders, dementia, drug-induced psychotic disorder, paranoid personality disorder, and hypochondriasis, have to be ruled out when diagnosing DD. [4]

The estimated lifetime prevalence of DD is approximately 0.2% in the general population and 2-3 % in patients with psychotic disorders, with a similar distribution in men and women. [5] [6] The onset of DD is generally in the middle to late adult life (earlier in males), and its course is highly variable, ranging from rapid and complete recovery to a chronic condition. [6]

Intrinsic clinical features of the disorder, including intransigent nature [7], as well as limited evidence-based literature, that consists of single case reports or small uncontrolled case series, hamper the management of DD. [8] Indeed, its treatment is anecdotal, mostly deduced by schizophrenia guidelines [3] [9] and based on antipsychotics as first-line drugs. Although pimozide, a first-generation antipsychotic (FGA), has been traditionally considered the first choice [10] [11][12], evidence supporting this option is rather scarce [13] [14] [15], mostly based on the results of a single small non-randomized clinical trial [13], limited to patients suffering from different forms of delusional parasitosis. [14] Moreover, the lack of evidence of its effectiveness in DD compared to other antipsychotics pointed out by a Cochrane systematic review [15], in addition to significant adverse effects, including extrapyramidal symptoms (EPS) and cardiovascular abnormalities, discouraged the use of pimozide. Furthermore, only a few case reports have documented the effectiveness of second-generation antipsychotics (SGA) in DD, including risperidone, olanzapine, quetiapine, and amisulpride. [16] [17][18][19][20][21][22] [23][24] Overall, the literature on the response to antipsychotic treatment in DD is inconsistent, with earlier literature suggesting a positive response in nearly 50% of the patients and similar effectiveness for FGA and SGA [25] [26] and a recent

systematic review indicating a good response only in 33.6% of patients (with FGAs outperforming SGAs, respectively 38.9% vs 27.7% response rate). [3] The heterogeneity of these findings could be partly explained by the non-compliance in treatment response to antipsychotics in DD, with secondary non-adherence (after starting the treatment) mainly due to drug side-effects. [27]

Recently, several case reports on the use of aripiprazole in the treatment of DD have been published. [28][29][30][31][32] Aripiprazole, a third-generation antipsychotic (TGA) that differs from SGA for its partial D2 agonist properties, is effective and well-tolerated in the treatment of psychosis in schizophrenia spectrum disorders as well as in other mental illnesses with predominant hallucinations, including obsessive-compulsive disorder, olfactory reference syndrome. [1] [33]

Given the poor response to pharmacological treatment of DD, evidence-based treatment is needed. Although the use of aripiprazole in this condition has a solid theoretical background, only anecdotal evidence of its clinical use exists. Here, we aimed to systematically review and summarize previous literature to evaluate the efficacy and tolerability of aripiprazole in delusional disorders.

METHODS

A comprehensive literature search was performed in PubMed, Cochrane Database of Systematic Reviews, and Scopus with the following keyword: ("delusional disorder AND aripiprazole"). Also, the reference lists of included papers were screened for snowball search. Studies were included if 1) reported the use of aripiprazole in patients affected by delusional disorders according to the DSM-5 or ICD-10; 2) a qualitative measure of outcome was present; 3) were written in English language. Commentaries, editorials, and reviews were excluded. All the articles published until February 2020 were included, while no publication status restrictions were imposed. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [34] for systematic review were followed (Figure 1). Every reference was screened by at least two researchers independently (AM and BS), any disagreement was discussed between the two and whenever it was not possible to make a decision, a third researcher was involved in the discussion. Once the full-text articles were selected, the data retrieved have been entered into a spreadsheet. Sample size, demographics, previous treatment, treatment response, adverse effects, and follow-up time were extracted. The analysis of the data was made by comparison. The heterogeneity of the results

such as the type of studies identified did not allow us to perform a meta-analysis, so a narrative synthesis was considered to be the best approach to describe and analyze the results.

RESULTS

The database search, after duplicates removal, brought a total of 94 records. Following the inclusion/exclusion criteria, the screening resulted in the inclusion of 19 full-text articles (Figure 1). The evidence available regarding the use of aripiprazole to treat delusional disorders is limited to case reports, with a total of 21 cases of DD treated with aripiprazole. [31][35] [36] [37][38] [39][40] [28] [1] [41] [29][8][16] [42][43] [44] [45][46] Information about the patients such as demographics, previous treatment, treatment response, adverse effects, and follow-up time were extracted and summarized in a table (see Table 1). Patients with DD (16 women and 5 men) had a mean age of 52.7 years (range: 17-85), comorbid cardiovascular (QT prolongation, hypertension, angina pectoris), metabolism (diabetes mellitus, osteoporosis), autoimmune (systemic lupus erythematosus) and neurological (multiple sclerosis, generalised tonic-clonic seizures - GTCS) disorders. The average illness duration of DD was 3.4 years (range: 0.2-7) and the type of delusion was somatic (57.1%), persecutory (19.1%), erotomanic (9.5%), and jealous (14.3%). The 85.7% of the patients were previously treated with antipsychotics other than aripiprazole: 27.8% were treated with FGA [haloperidol (11.0%), sulpiride (5.6%), pimozide (5.6%), amisulpride (5.6%)], and 72.2% with SGA [risperidone (33.3%), olanzapine (33.3%), paliperidone (5.6%)]. These switched to aripiprazole for lack of response and/or tolerability issues including extrapyramidal symptoms, weight gain, galactorrhea, QT prolongation. Occasionally, antidepressant treatment was also prescribed.

All studies reported patient clinical improvements after the beginning of the treatment with aripiprazole. The mean dose of aripiprazole was 11.1 mg/day (range: 1.5 to 30). It was used as monotherapy (66.7%), and in combination [28.6% with antidepressant medications: venlafaxine (4.8%), mirtazapine (14.2%), imipramine (4.8%), not specified antidepressant (4.8%); 4.8% with sodium valproate for GTCS; 4.8% psychological therapy]. The average time to achieve a response based on the clinician's impression was 5.7 weeks (0.5 to 17.1). Adverse effects were reported in 19% of the cases and included asthenia (i.e. weakness and/or muscle fatigue), extrapyramidal symptoms (akathisia and parkinsonism), hyperprolactinemia (galactorrhea and amenorrhea), and insomnia. No serious adverse events were reported.

DISCUSSION

This is the first systematic review on the use of aripiprazole in DD. Although the literature is sparse with no randomized controlled trials, our findings suggest that aripiprazole can be an effective, safe, and well-tolerated treatment for DD.

Previous evidence shows that antipsychotics are effective in DD with a response rate of 50%. [25] We found that aripiprazole was effective and used mostly in monotherapy, with a mean dosage below the defined daily dose (15 mg/day per os). [47] Almost all patients switched from SGA and FGA to aripiprazole for either lack of effectiveness or adverse effects. Furthermore, the combination of aripiprazole with antidepressants was also effective in the somatic type of DD cases (see below).

Compliance is a crucial factor regarding the prognosis of delusional disorder. A lack of insight and a well-conserved social and socio-occupational functioning can contribute to reduce it. Moreover, the side effects of antipsychotic drugs, particularly FGAs, can exacerbate poor adherence. [26] Although aripiprazole showed an all-cause discontinuation rate in multiple episode schizophrenia that is similar to SGAs [33], we found adverse effects in 19% cases of DD, with extrapyramidal symptoms (akathisia and parkinsonism), hyperprolactinemia and insomnia being the most severe conditions and with no serious adverse events. Notably, these patients had several medical comorbidities and reported adverse effects from previous treatments. One patient reported hyperprolactinemia with galactorrhea and amenorrhea that subsided only after stopping the drug. Although aripiprazole is frequently used for the management of antipsychotic-induced hyperprolactinemia [48], it may also raise prolactin levels in less than 5% of patients. [49] This effect, which may be associated with specific genetic variations [50], is mediated by agonist effects on serotonin signaling. Indeed, clinicians may have likely selected aripiprazole based on its tolerability with low potential for extrapyramidal symptoms, weight gain, cardiac effects, sedation, prolactin elevation, and seizures. [51][52] [53] The availability of a long-acting injectable formulation, and the tolerability of aripiprazole can improve adherence and consequently the prognosis in DD, as shown by Diefenderfer and colleagues. [1]

Aripiprazole has partial agonist properties on dopamine D2 and D3 receptors and serotonin 5 HT1A receptors, and antagonist effects on 5HT2A. [54][55][28] The modulation of dopamine and serotonin signaling can explain the effectiveness of aripiprazole in DD. Indeed, aripiprazole has a unique pharmacologic profile, being a partial dopaminergic agonist that acts on both pre- and postsynaptic D2 receptors that have been implicated in psychotic

symptoms. On these receptors, aripiprazole can have several effects, including weak stimulation (so-called "partial" agonist), inhibition (antagonist), and full stimulation (agonist), depending on the sensitivity of the receptors and on the availability of dopamine. [56][57] The partial agonism of aripiprazole at D2 receptors may contribute to a reduced risk for EPS, which can be diagnosed only in 10% of patients treated with high doses, and particularly akathisia. [58][59] [60][61]

Evidence shows that serotonergic deficit may also play a role in DD. Different classes of antidepressants acting on serotonin signaling were effective in monotherapy or in combination with antipsychotics in the treatment of DD. [62][63][64][65][35] Moreover, aripiprazole can modulate serotonin pathway with its 5HT1A and 5HT2A receptor agonist function. These effects on the serotonin system may explain the efficacy of this drug in delusional disorder somatic type (DDST), in which serotonin dysfunction has been hypothesized. [63] [62] Serotonin 5-HT1A partial agonist and serotonin 5-HT2C functional antagonist properties of aripiprazole can also enhance dopamine release indirectly in the prefrontal cortex through the activation of serotonin pathways in the nucleus accumbens, and this can positively contribute to its direct modulation of dopamine signaling. Overall, the efficacy of aripiprazole in DDST can be due to its modulation of the D2 pathway as well as its enhancement of serotonin activity. [35][66]

Aripiprazole is generally well-tolerated even with comorbid medical conditions. The cardiometabolic side effects of aripiprazole are uncommon compared with SGAs. Indeed, aripiprazole shows a lower risk to induce metabolic syndrome and does not affect glucose concentration and lipid profiles.[67][68][69][70][71] Also, treatment with this drug is rarely associated with QTc prolongation. [72] Aripiprazole can also be useful in the treatment of psychosis in patients with comorbid hyperprolactinemia, including prolactinoma. [73] When epilepsy is comorbid, aripiprazole can be safe with a risk of seizures of about 0.1%, which is the lowest among SGA/TGA agents. [29][74] For example, Garg and coworkers, underscore the effectiveness of aripiprazole in a persistent delusional disorder with co-morbid epilepsy that failed to respond to three courses of different SGAs and two FGAs [29].

LIMITATIONS

This approach has some limitations. The retrospective and uncontrolled design of the studies (case reports) does not allow quantitative estimation of the effects of aripiprazole. Moreover, case reports have an inherent publication bias favoring positive results; therefore, a generalization of these findings cannot be done without caution. Although a series of cases is

suggestive of a possible effect of aripiprazole in DDs, randomized controlled trials are warranted to confirm these results. Also, the clinical evaluation of patients was heterogeneous across studies and mostly based on clinic-based impressions. Nonetheless, given the low prevalence and the intrinsic psychopathological features of DD (e.g. lack of insight, suspiciousness) that limit the ability to recruit patients for clinical studies, the evidence here provided is suggestive of the effectiveness of the drug. Nonetheless, a systematic approach and a relatively large number of case studies should limit these biases.

CONCLUSIONS

Given its effectiveness, safety, tolerability and the availability of long-acting injectable formulation, aripiprazole could be a viable treatment for delusional disorder. Further research providing quantitative results on the use of aripiprazole even compared to other antipsychotics for the treatment of delusional disorder through other and more consistent studies, such as randomized controlled trials, is needed.

DISCLOSURES

Conflicts of interest: none

CRediT author statement

Alessandro Miola (AM): Conceptualization, Methodology, Data curation, Writing- Original draft preparation. Benedetta Salvati (BS): Data curation, Writing- Reviewing and Editing. Fabio Sambataro (FS): Conceptualization, Methodology, Supervision, Writing- Original draft preparation. Tommaso Toffanin (TT): Conceptualization, Writing- Reviewing and Editing.

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First author and year	Age (ys), gender	Type of delusional disorder	Duration of illness (ys)	Comorbidity	family history	Previous treatment for DD	Efficacy/Tolerability of past treatments	Initial treatment (maximum dosage)	Treatment course	Side effects	Other treatment	Response	Follow up	Neuroimaging and tests
Myers et al, 2004 [31]	17, F	Erotomanic	N/A	Negative	Negative	None	N/A	Aripiprazole 10 mg/day	Aripiprazole 10 mg/day	None	Cognitive and family therapy	By week 2 improvement and by week 8 maximal pharmacological improvement	Self-reported; duration: 5 months. Clinical improvement	None
Smith et al, 2009 [43]	41, F	Erotomanic	6	Multiple sclerosis	N/A	None	None	Aripiprazole 15 mg/day	Aripiprazole 15 mg/day and antidepressants (not specified)	None	None	Significant improvement in delusions after 1 week.	Discontinued by the patient after 2 months	MRI and lumbar puncture were suggestive of demyelinating disease.
Duvar et al, 2010 [28]	64, F	Jealous accompanied with major depressive disorder	N/A	N/A	N/A	1. Sertraline 50 mg/day and olanzapine 15 mg/day; 2. Risperidone 4 mg/day	1. Poor treatment response for 2 months, and weight gain; 2. Poor treatment response for 2 months, EPS (rigidity and tremor)	Venlafaxine was titrated up to 225 mg/day, and aripiprazole to 30 mg/day	Aripiprazole 30 mg/day and Venlafaxine for 3 months; dose reduced to 10 mg/day for delusions improvement and continued for 1.5 years.	None	None	15 days of treatment partial response;	Full recovery after 1.5 years	Brain MRI was normal.
Jayaram et al, 2011 [32]	29, F	Jealous	7	pituitary microadenoma	N/A	Amisulpride 200 mg/day for 2 weeks	galactorrhea	Aripiprazole 15 mg/day	Aripiprazole 30 mg/day	None	None	Improvement in both galactorrhea and psychopathology after 3 months	N/A	Brain MRI showed a pituitary microadenoma that was stable at 23 months follow up. No compression on the surrounding structures was noted. Baseline serum prolactin was 45.5 ng/mL (1.2–19.2 ng/mL), after 3 months it was 28.5 ng/mL
Joseph et al, 2016 [45]	36, F	Jealous	2	Negative	N/A	None	None	Aripiprazole 5 mg/day	Aripiprazole 15 mg/day	Galactorrhea, amenorrhea	None	By week 3 improvement	Still in remission after 1 month of aripiprazole discontinuation. Three months later, a psychotic relapse that responded positively to aripiprazole 10 mg/day, but discontinued for hyperprolactinemia	Neuroimaging to rule out a prolactinoma. Serum prolactin levels were normal at baseline, increased after aripiprazole titration, and normalized after aripiprazole discontinuation, respectively
Diefende	29, F	Persecutory	7	Past psychotic	N/A	Quetiapine,	N/A	Aripiprazole	Aripiprazole long-	None	Mirtazapine 15	N/A	Full resolution	N/A

First author and year	Age (ys), gender	Type of delusional disorder	Duration of illness (ys)	Comorbidity	family history	Previous treatment for DD	Efficacy/Tolerability of past treatments	Initial treatment (maximum dosage)	Treatment course	Side effects	Other treatment	Response	Follow up	Neuroimaging and tests
rfer et al, 2018 [1]				disorder not otherwise specified, and substance use (cannabis)		haloperidol, and citalopram not reported dose, olanzapine 10 mg and risperidone 4 mg		tablets 5 mg and i.m. 9.75 mg immediate release for 2 days	acting injection 300 mg after 2 days		mg/day to treat depressive symptoms		after 10 months	
Garg et al, 2014 [29]	22, M	Persecutory	2	Generalized tonic-clonic seizures (GTCS).	Negative	Sodium valproate for GTCS, risperidone, olanzapine, ziprasidone, haloperidol, trifluoperazine	EPS with typical antipsychotics and 1 episode of GTCS with risperidone 4 mg/day	Aripiprazole 5 mg/day and sodium valproate 1g/day	Aripiprazole 20 mg/day over 6 weeks and sodium valproate 1g/day	None	None	Improvement after 4 weeks	N/A	The laboratory test and brain imaging were negative
Miyamoto et al, 2008 [8]	60, F	Persecutory	0.2	Negative	Negative	None	None	Aripiprazole from 3 mg/day up to 9 mg/day	Aripiprazole 3 mg/day	Parkinsonism at 2 months with 9 mg/day dose; Akathisia at 2 months with 6 mg/day	None	Improvement after 4 months	N/A	Her laboratory examination and computed tomography of the brain did not show any abnormalities.
Iannuzzi et al, 2019 [44]	84, M	Persecutory	3	Charles Bonnet syndrome (benign visual hallucinations in individuals with significant vision loss), macular degeneration, atrial fibrillation, coronary artery disease, hyperlipidemia, and prostate cancer in sustained remission.	N/A	Risperidone 4 mg/day	Poor response and QTc prolongation	Aripiprazole 5 mg/day	Aripiprazole 5 mg/day	None	None	Improvement rapid and robust within 5 days.	Full remission after 4 months	CT scan showed multiple lacunar brain infarcts. Mild cognitive impairment at the Neuropsychological testing
Dimopoulos et al, 2008 [35]	51, F	Somatic	6	Negative	Grandmother with AD and an aunt diagnosed with schizophrenia	1) Haloperidol 15 mg/day; 2) Olanzapine 15 mg/day and divalproex 1000 mg/day; 3) Mirtazapine 60 mg/day;	N/A	Mirtazapine 90 mg/day added to aripiprazole 15 mg/day after 2 weeks	Mirtazapine 90 mg/day, aripiprazole 15 mg/day	N/A	N/A	N/A	Clinical observation; Duration 3 months. Clinical improvement	None
Bennassar et al, 2009 [37]	42, F	Somatic (primary delusional parasitosis)	2	Lupus erythematosus	N/A	N/A	N/A	Aripiprazole 5 mg/day	Aripiprazole 10 mg/day	None	N/A	In a 1-month follow up visit, she explicitly said that	Complete remission 6 months	N/A

First author and year	Age (ys), gender	Type of delusional disorder	Duration of illness (ys)	Comorbidity	family history	Previous treatment for DD	Efficacy/Tolerability of past treatments	Initial treatment (maximum dosage)	Treatment course	Side effects	Other treatment	Response	Follow up	Neuroimaging and tests
												parasites no longer troubled her.		
Benassar et al, 2009 [37]	49, M	Somatic (primary delusional parasitosis)	3	HIV and substance abuse	N/A	N/A	N/A	Aripiprazole 5 mg/day	Aripiprazole 15 mg/day	None	N/A	Symptom resolution after 2 weeks and maintained.	1 month in remission	N/A
Carpiniello et al, 2011 [39]	72, M	Somatic (primary delusional parasitosis)	2	HPN, DM, CKD	None	Risperidone 2 mg/day	Sedation	Aripiprazole 10 mg/day	Aripiprazole 15 mg/day	Midterminal insomnia	Quetiapine 12.5 mg/day for a month to treat insomnia	N/A	10 months stable condition	MRI showed different areas of altered signal, hyperintense in FLAIR, and T2 and DP, in the periventricular white matter, in frontoparietal subcortical left and right areas and semioval centers due to chronic vascular hypoperfusion, in addition to the expansion of the ventricular system and of cortical and cisternal spaces due to cerebral atrophy.
Freudenmann et al, 2010 [41]	27, F	Somatic (primary delusional parasitosis)	4.5	Past use of substances (amphetamine, cannabis, ecstasy, alcohol)	N/A	risperidone and paliperidone 6 mg/day	Weight gain (20 kg)	Aripiprazole 10 mg/day	Aripiprazole 10 mg/day	None	None	N/A	Partial improvement at 3 and 6 months telephone follow up	MRI, EEG, CSF examination, urine drug screening, and routine blood tests were unremarkable. Selective frontal impairment at the neuropsychological testing.
Huang Wet et al, 2013 [38]	67, M	Somatic (secondary delusional parasitosis)	2	HPN, DM, Cataract, CKD	Early dementia	Sulpiride 200 mg/day	Severe dizziness	Aripiprazole 3.75 mg/day	Aripiprazole 7.5 mg/day	None	N/A	Improvement at 2 weeks and complete resolution after one month.	1-month remission	MMSE was 19 and showed brain atrophy (CT).
Ponson et al, 2015 [40]	68, F	Somatic (delusional infestation)	2	Past posttraumatic stress disorder symptoms after the death of her mother lasting 3-4 years	N/A	None	N/A	Aripiprazole 5 mg/day	Aripiprazole 15 mg/day	None	None	Partial response after 2 months	Full recovery at 8 months	Antipsychotic treatment reduced supplementary motor area activation during mental facial imagery task measured using fMRI

First author and year	Age (ys), gender	Type of delusional disorder	Duration of illness (ys)	Comorbidity	family history	Previous treatment for DD	Efficacy/Tolerability of past treatments	Initial treatment (maximum dosage)	Treatment course	Side effects	Other treatment	Response	Follow up	Neuroimaging and tests
Rocha et al, 2006 [16]	85, F	Somatic (primary delusional parasitosis)	5	HPN, osteoporosis	N/A	1. Pimozide 6 mg/day Olanzapine 5 mg/day	1. EPS 2. Hyponatremia	Aripiprazole 15 mg/day	Aripiprazole 7.5 mg/day	Asthenia with aripiprazole 15 mg/day	None	Full recovery at 4 months	N/A	MRI showed cerebral atrophy compatible with age. Normal MMSE and CDT.
Sandoz et al, 2008 [42]	54, F	Somatic (primary delusional parasitosis)	5	None	N/A	Olanzapine	Weight gain	Aripiprazole 20 mg/day	Aripiprazole 10 mg/day	None	None	Improvement after 2 to 3 weeks	Full remission after 1 year	N/A
Umezaki et al, 2017 [46]	72, F	Somatic (oral cenesthopathy)	2	Negative	Negative	Amitriptyline 10 mg/day	Poor treatment response	Aripiprazole 1.5 mg/day	Aripiprazole 1.5 mg/day	None	None	By week 8 improvement	14 months remission	SPECT revealed a right > left frontal, temporal and thalamus asymmetric rCBF that was attenuated 14 months later. MRI showed no atrophy or infarction.
Umezaki et al, 2017 [46]	73, M	Somatic (oral cenesthopathy)	3	Angina pectoris, DM, and osteoporosis	Negative	None	None	Aripiprazole 1 mg/day	Aripiprazole 1.5 mg/day	Sleep disturbance	Mirtazapine 7.5 mg/day titrated up to 45 mg/day to treat insomnia	N/A	14 months remission	SPECT revealed a right > left frontal, temporal, and thalamus asymmetric rCBF that was attenuated 14 months later.

Table 1. Cases treated with aripiprazole for delusional disorders sorted by predominant delusion type reported by the patient. AD, Alzheimer's Disease; CDT, Clock Drawing Test; CKD, Chronic Kidney Disease; DM, Diabetes Mellitus; EPS, extrapyramidal symptoms; GTCS, generalized tonic-clonic seizures; HPN, hypertension; MDD, Major Depressive Disorder; MMSE, Mini-Mental Status Examination

Legends of Figures

Figure 1. Preferred Reporting Items For Systematic Reviews (PRISMA) flow diagram

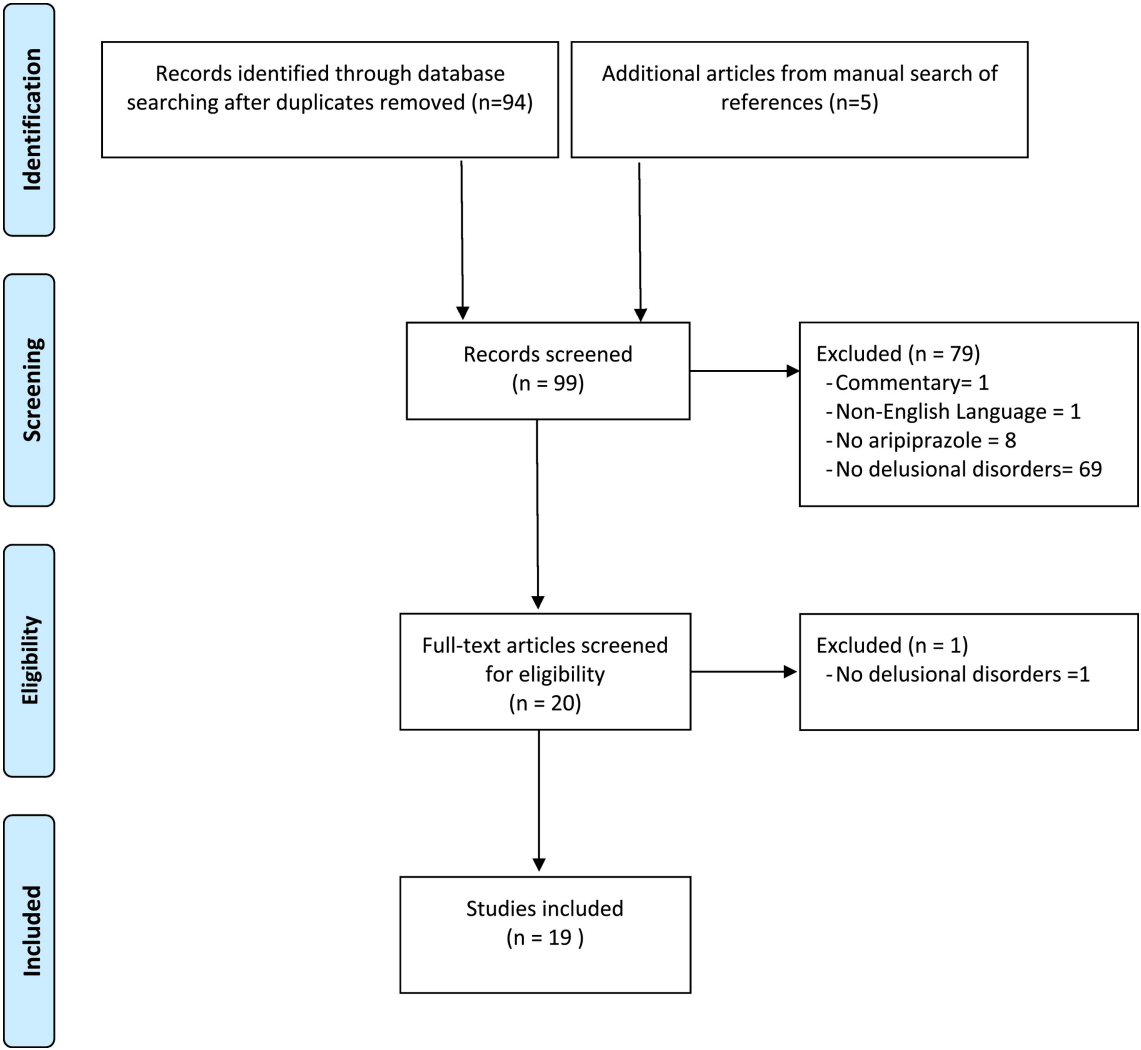
Identification
Screening
Eligibility
Included
Records identified through database searching after duplicates removed (n=94)
Additional articles from manual search of references (n=5)
Records screened (n = 99)
Excluded (n = 79)
- Commentary= 1
- Non-English Language = 1
- No aripiprazole = 8
- No delusional disorders= 69
Full-text articles screened for eligibility (n = 20)
Excluded (n = 1)
- No delusional disorders =1
Studies included (n = 19)

Figure 1