

Antipsychotics in Hyperthyroid-Related Psychosis: Case Report and Systematic Review

Danielle GOLUB¹, Victor RODACK¹

¹ Department of Psychiatry, NYU School of Medicine, 550 1st Avenue, New York, NY, 10016, USA

Correspondence to: Danielle Golub, 225 E. 34th Street, Apt 5J, New York, NY, 10016
E-MAIL: Danielle.Golub@nyumc.org

Submitted: 2018-02-02 Accepted: 2018-04-15 Published online: 2018-04-22

Key words: **Hyperthyroidism; Graves Disease; Antipsychotic Agents; Psychotic Disorders; Delusions; Hallucinations**

Neuroendocrinol Lett 2018; **39**(1):65–74 PMID: 29803209 NEL390118A12 ©2018 Neuroendocrinology Letters • www.nel.edu

Abstract

OBJECTIVES: Hyperthyroidism has been associated with relatively rare presentations of psychotic symptoms. We report an example of the successful use of antipsychotics to manage psychotic symptoms in hyperthyroid-related psychosis. Furthermore, we systematically describe the available literature on the use of antipsychotics in this setting to determine the associated relative efficacies of the various antipsychotic agents.

METHODS: Presentation of a case of hyperthyroid-related psychosis treated with an antipsychotic agent followed by a systematic review of all similar cases: PubMed, Ovid MEDLINE and PMC were searched for articles published between 1960 and 2017 that report on the use of specific antipsychotics in the management of hyperthyroid-related psychosis.

RESULTS: An 81-year-old woman presented with hallucinations and delusions in the context of untreated Graves' Disease and was effectively treated with medical management of her thyroidopathy and psychopharmacologic management of psychotic symptoms. Systematic review revealed that typical and atypical antipsychotics have comparable efficacy in the management of psychotic symptoms in hyperthyroid-related psychosis.

CONCLUSION: Choice of antipsychotic in hyperthyroid-related psychosis should be primarily based on side-effect profile and medical comorbidities. Risperidone is the optimal and seemingly effective choice for treating hyperthyroid-related psychosis in an elderly thyrotoxic patient.

Abbreviations:

PRISMA	- Preferred Reporting Items for Systematic Reviewers;	EPS	- Extrapyramidal Symptoms;
CARE	- Case Report Guidelines;	SPECT	- Single Photon Emission Computed Tomography;
TSH	- Thyroid-Stimulating Hormone;	PO	- Per Os/By Mouth;
ECG	- Electrocardiogram;	IM	- Intramuscular;
CT	- Computerized Tomography;	n/a	- Not available
VDRL	- Venereal Disease Research Laboratory;	μIU/mL	- micro international units per milliliter;
FT3	- Free Triiodothyronine;	pg/mL	- picograms per milliliter;
FT4	- Free Thyroxine;	ng/dL	- nanograms per deciliter;
MoCA	- Montreal Cognitive Assessment;	IU/mL	- international units per milliliter;
LBD	- Lewy Body Dementia;	mg	- milligrams

INTRODUCTION

Graves' Disease is an autoimmune disease that causes hyperthyroidism and affects 1-3% of the general population (Cooper & Stroehela, 2003). Common symptoms of hyperthyroidism include tachyarrhythmia, heat intolerance and weight loss, as well as psychiatric symptoms including anxiety, irritability, fatigue and insomnia. Occasionally, severe psychiatric symptoms such as mania or psychosis can occur (Bunevicious & Prange Jr, 2006). Limited literature exists regarding the choice and efficacy of antipsychotics in managing hyperthyroidism-induced psychosis.

We report the case of an elderly woman presenting with laboratory-proven hyperthyroidism and psychotic symptoms who was treated successfully with both anti-thyroid and antipsychotic agents. We further explore the factors in choosing an antipsychotic for the management of psychosis secondary to hyperthyroidism based on a systematic review of the literature.

METHODS

A systematic review was performed as further described below in sections 2.1–2.3 using the methodology for the collection and reporting of data outlined in the Preferred Reporting Items for Systematic Reviewers (PRISMA) statement (Moher *et al.* 2010).

Search Question, Primary Outcome, Inclusion and Exclusion Criteria

The question posed for systematic review was: What is the effectiveness of antipsychotics in the management of hyperthyroid-related psychosis? All studies, including case reports and case series, based on human subjects and published in the English language were included. An all-inclusive search was conducted based on findings of the initial search of PubMed by primary author revealing a paucity of literature.

The primary outcome measure was control of psychiatric symptoms in psychosis secondary to hyperthyroidism, defined as: complete control (total remission of symptoms indefinitely), moderate control (total remission of symptoms for given period of time), mild control (relief of some, but not all psychiatric symptoms), and failure (no change in psychiatric symptomatology). This qualitative symptomatic response grading was used given the heterogeneous nature of the treatment response data reported within the studies found. Secondary outcome measures were the rate of effectiveness of both typical and atypical antipsychotics as first line treatment in hyperthyroid-related psychosis, the rate of effectiveness of combination therapy in hyperthyroid-related psychosis, and the incidence of use and relative efficacy of each individual antipsychotic in management of psychiatric symptoms in hyperthyroid-related psychosis.

Studies eligible for inclusion met the following criteria: (1) patients had a definitive diagnosis of hyperthyroidism (of any etiology) (2) patients demonstrated psychotic symptoms including hallucinations, delusions or disorganized thought process in conjunction with presentation of hyperthyroidism. (3) antipsychotic(s) were used with the intention of managing psychotic symptoms (4) the antipsychotic(s) used were specified in the paper. Exclusion criteria involved (1) non-human studies and (2) non-English publications.

Search Strategy and Study Selection

PubMed, MEDLINE, and PMC were searched using individualized search strategies for each database. The search strategy for PubMed can be seen in Appendix A of the supplementary material, with a similar search strategy for the other databases. Reference lists of all publications were additionally reviewed for relevant studies on the use of antipsychotics in hyperthyroid-related psychosis.

A two-step review of all articles returned by our search strategies was performed. First, two reviewers independently screened all titles, abstracts, and full text of the returned articles to decide if they met the inclusion criteria. Secondly, any discrepancies between the two reviewers was resolved by discussion. The search process uncovered 26 peer-reviewed articles comprised of case series and case studies published from 1960 to 2017.

Data Collection and Quality Assessment

Data was extracted independently by two reviewers from the selected articles and stored in an electronic database. Data fields included: type of study (case report or case series), patient age, first and second-line choice of antipsychotic agent, associated dose and route of antipsychotics used, duration of treatment with given antipsychotic, and the primary outcome, as defined in section 2.1, associated with each antipsychotic. The study quality was assessed according to the CARE guidelines for case reports (Gagnier *et al.* 2013). We evaluated the quality of included studies in terms of adherence to the CARE guidelines checklist: those studies that met at least 9 out of 13 criteria (70%) were considered moderate or high-quality studies and consequently were included in our review.

CASE REPORT

An 81-year-old English-speaking Filipino female with medical history significant for untreated bilateral cataracts and without known psychiatric history was brought in by family for worsening psychosis of unknown etiology and for malnutrition. The patient had been living independently for over 40 years, but approximately 10 years prior to her initial presentation, her siblings began to notice signs of behavior change and increasing paranoia. The patient had suddenly

retired from her job, stopped participating in her regular charity work, and barely ever left her home. Over the next several years, the patient became increasingly suspicious of her siblings and eventually would not allow them into her home. After not hearing from her for two years, the family came to her apartment to find the patient emaciated, staring at the ceiling, talking to herself, surrounded by numerous food containers, garbage and unopened mail. Over the next several weeks, the patient continued to refuse to eat, sleep very little, stare blankly at bare walls, and became fixed in a delusion that that her siblings were part of a "cartel" trying to steal from her. There was no history of psychiatric disorders in the patient's family, and she had no known toxic habits such as alcohol or drug use. After an episode of aggression in which the patient began violently throwing household objects at her siblings, one of them brought her to the hospital to be evaluated.

The patient was initially admitted to the medicine service for failure to thrive given her cachectic appearance. Initial labs were significant for low serum protein and albumin, mild leukopenia, and a thyroid-stimulating hormone (TSH) level below the detectable range (<0.008 $\mu\text{IU/mL}$). Her vital signs were notable for widened pulse pressure (140-170s/50-70s), but physical exam on admission was unremarkable without evidence of palpable thyromegaly or thyroid nodules, exophthalmos, lid lag, skin changes, pathologic heart sounds, tremor, psychomotor agitation or retardation, muscle rigidity or gait abnormalities. Electrocardiogram (ECG) was likewise benign (sinus rhythm), non-contrast head CT was without acute intracranial pathology, and infectious workup was negative: normal chest x-ray, bland urinalysis and negative blood cultures. Additional lab testing otherwise revealed a non-significant vitamin B12 level (518pg/mL), liver function tests and other serum electrolytes within normal range, and a negative VDRL. Further workup of low TSH demonstrated correspondingly high serum thyroid hormone levels (free thyroxine [FT4]: 3.2 ng/dL, free triiodothyronine [FT3]: 6.7 pg/mL) and serum antibody screen revealed a thyroid peroxidase antibody level of 329 IU/mL (reference range <35 IU/mL) and a thyroid-stimulating immunoglobulin antibody level of 419% above basal activity (reference range $<140\%$), all most consistent with Graves' autoimmune thyroidopathy. Atenolol 50 mg daily and methimazole 5 mg daily were initiated on hospital day 1 for the treatment of presumed Graves' Disease and continued throughout the patient's hospital course. Thyroid ultrasound findings of a hyperemic right lobe with diffuse changes in echotexture throughout the thyroid gland further supported a diagnosis of Graves' Disease.

Despite initiation of antithyroid treatment and relatively swift attenuation of thyroid hormone levels (FT4: 2.08 ng/dL and FT3: 5.8 pg/mL by hospital day 4), the

patient continued to complain of nearly constant visual and auditory hallucinations and demonstrate paranoid and persecutory delusional thinking. For example, she reported intermittently seeing flashing lights, seeing images of famous people laughing around her and seeing horse-drawn carriages flying across the room. She additionally heard the voices of her parents describing the evil nature of her siblings. Nevertheless, she was consistently alert and oriented to person and place, with reactive affect and organized thought process on mental status exam, however with profound lack of insight into her psychiatric symptoms, and on psychometric assessment, she scored an equivalent of 26 out of 30 (adjusted for vision loss) on the Montreal Cognitive Assessment (MoCA), with a deficit only in delayed recall. With the help of the psychiatry consult service, risperidone 0.5 mg twice daily was initiated on hospital day 4 for management of her psychotic symptoms.

Over the next couple days, the patient reported resolution of her auditory hallucinations as well as improved sleep and appetite. On hospital day 6, given its initial efficacy, risperidone was titrated up to 1 mg twice daily. The patient remained oriented, cooperative, linear and future-oriented on mental status exam, but continued to demonstrate poor insight, endorse some visual hallucinations, although with decreased frequency, and express delusional and paranoid thinking, in particular about her family. Given that the safest discharge plan for this patient was determined to be to home with her siblings to help with her activities of daily living because of her limited sight and recent history of being unable to care for herself, it was crucial that psychiatric symptoms resolve such that the patient would be able to accept living with her siblings. On hospital day 11, risperidone was again uptitrated to 1.5 mg twice daily. Over the following few days, the patient's visual hallucinations resolved and her symptoms of paranoia and delusions became less conspicuous. She became able to demonstrate insight into her medical illness and how it may have contributed to her perceptual symptoms, and was able to discuss her suspicions of some of her siblings as related to long-standing sibling rivalry rather than participation in a persecutory cartel.

The discharge diagnoses for this patient included psychotic disorder due to another medical condition, with delusions vs. hallucinations (DSMV 293.81, 293.82), in this case suspected to be secondary to uncontrolled hyperthyroidism. She was discharged after a 16-day hospitalization with resolving thyroid hormone levels (FT4: 1.83 ng/dL, FT3: 4.9 pg/mL) and improved psychotic symptoms without perceptual disturbances after 13 days of risperidone treatment. Discharge medications included risperidone 1.5 mg twice daily for continued management of psychosis, and methimazole and atenolol for her thyroidopathy.

RESULTS

To our knowledge, there are currently no studies that have addressed the relative efficacies of antipsychotics in the treatment of psychosis related to hyperthyroidism. While definitive treatment of the psychosis is achieved with medical or surgical intervention on the underlying thyroidopathy, acute control of severe psychiatric and behavioral symptoms is generally necessary (Brownlie *et al.* 2000). The results of the search strategy defined in the methods section is summarized in Figure 1. Overall, a total of 1,752 articles were identified, and after application of the inclusion and exclusion criteria, 44 were determined to fit the criteria. After removal of duplicates, there were a total of 26 related articles published between 1960 and 2017. This included 25 case reports and 1 case series comprising a total of 28 documented cases of specific antipsychotics used in the management of hyperthyroid-induced psychosis.

A summary of the data extracted from this systematic review of the literature can be seen in Table 1 (Bianco & Lerro, 1972; Bursten, 1961; Caudill & Lardinois, 1991; Corn & Checkley, 1983; da Silva *et al.* 2009; Dahale *et al.* 2014; Emul *et al.* 2013; Greer & Parsons, 1968; Hafner & Schloch, 2017; Hazen *et al.* 2015; Katsigiannopoulos *et al.* 2010; Kobayashi *et al.* 2011; Lee

et al. 2013; Macedo *et al.* 2012; Mahmood *et al.* 2005; Marian *et al.* 2009; Memon *et al.* 2016; Muramatsu & Ahmed, 2013; Nibuya *et al.* 2002; Oshikubo *et al.* 2015; Ozten *et al.* 2013; Singh & Gupta, 2007; Snabboon *et al.* 2009; Ugwu *et al.* 2017; Urias-Urbe *et al.* 2017; Yang *et al.* 2003). Typical antipsychotics (trifluoperazine, thioridazine, levomepromazine, chlorpromazine, and haloperidol) were used as first-line agents in 64% of cases and were effective in completely resolving psychotic symptoms in 39% of those cases. Notably, failure of efficacy of typical antipsychotics, specifically haloperidol, as first-line agents was attributable to medication non-compliance in 27% of cases in which typical antipsychotics were used. Atypical antipsychotics (risperidone, aripiprazole, olanzapine and quetiapine), were used as first-line agents in 36% of reported cases, and were effective in completely resolving psychotic symptoms in 40% of cases, demonstrating essentially the same rate of efficacy as the typical antipsychotics (39%). Combined regimens, typically with the addition of a benzodiazepine or mood stabilizer, were used in 32% of all cases, and were effective in treating psychosis in 75% of cases. Four cases reported the trial of co-administration of multiple antipsychotic agents (haloperidol paired with either olanzapine, quetiapine or chlorpromazine, or risperidone and quetiapine) to

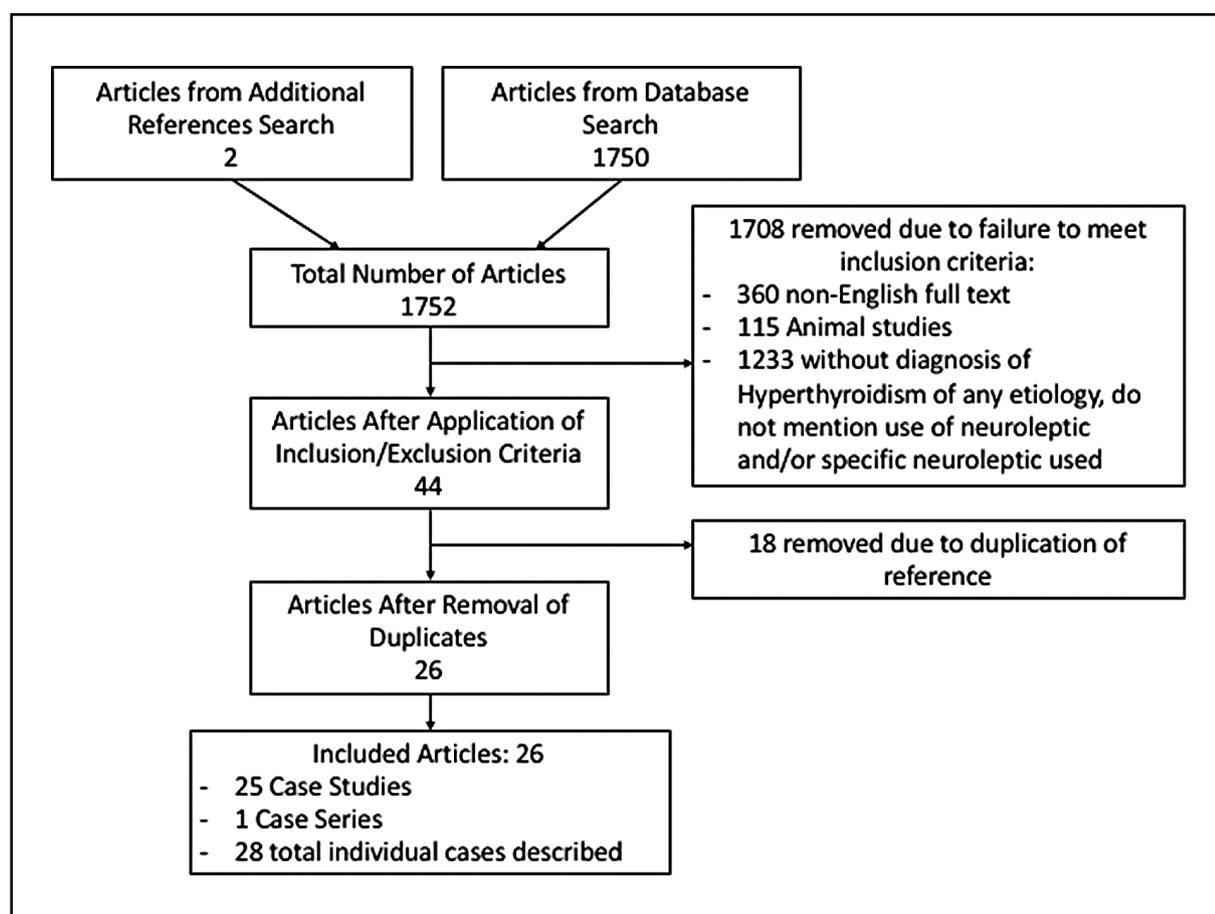


Fig. 1. Flow Diagram of Search Results

Tab. 1. Systematic Review of the Literature on the use of Neuroleptics in Psychosis Related to Hyperthyroidism

Author	Year	Study Design	Age	Psychiatric Symptomatology	First-Line Agent(s)	Dose (PO unless specified)	Duration	1° Outcome (Symptomatic Control)	Second-Line Agent(s)	Dose (PO unless specified)	Duration	1° Outcome (Symptomatic Control)
Bursten	1961	Case Series	46	Persecutory delusions, blunted affect, lack of insight	Trifluoperazine	n/a	n/a	Complete Control				
			44	Grandiose and paranoid delusions, flight of ideas, flat affect	Chlorpromazine	n/a	1 month	Failure	Electroconvulsive therapy	21 times	Over several months	Mild Control
			41	Grandiose delusions, hallucinations, incoherent speech	Chlorpromazine	n/a	1 month	Mild Control				
Greer and Parsons	1968	Case Report	28	Visual and auditory hallucinations, paranoid delusions	Chlorpromazine	400mg daily	2 weeks	Complete Control				
Bianco and Lerro	1972	Case Report	42	Paranoid delusions, loosening of associations, auditory hallucinations, inappropriate affect	Chlorpromazine	50mg four times a day	36 hours	Failure	Haloperidol	2mg two times a day	2-3 weeks	Complete Control
Corn and Checkley	1983	Case Report	46	Mania, paranoid delusions	Haloperidol	n/a	3-4 weeks	Complete Control				
Caudill and Lardinois	1991	Case Report	16	Agitation, paranoid delusions, visual hallucinations	Chlorpromazine	50mg every four hours	Several days	Failure	Haloperidol Thioridazine Thiothixene	n/a	2 weeks, at various intervals	Complete Control
Nibuya et al.	2002	Case Report	34	Disorganized thought process, paranoid delusions and delusions of reference	Haloperidol Chlorpromazine Thioridazine Levomepromazine	0-900mg chlorpromazine equivalents daily	Approximately 80 days	Failure	Electroconvulsive therapy	3 times	Several days	Complete Control
Yang et al.	2003	Case Report	48	Auditory hallucinations, mania	Haloperidol Lithium Clonazepam	5-11mg daily 900mg daily 2-5.5mg daily	2 weeks (haloperidol) 3 months (lithium, clonazepam)	Complete Control				
Mahmood et al.	2005	Case Report	25	Visual and auditory hallucinations	Risperidone	1mg two times a day	3 months	Complete Control				
Singh and Gupta	2007	Case Report	31	Paranoid delusions, inappropriate affect, auditory hallucinations	Risperidone Clonazepam	n/a	n/a	Failure (medication non-compliance)	Olanzapine Lorazepam Zolpidem	10-20mg daily 4-8mg daily 10mg nightly	4 weeks	Complete Control
Da Silva et al.	2009	Case Report	28	Paranoid delusions. flat affect Auditory hallucinations	Risperidone	2mg three times a day	2-3 weeks	Complete Control				
Snaboon et al.	2009	Case Report	40	Paranoid delusions, auditory hallucinations	Haloperidol Lorazepam	4-8mg daily 1-2mg daily	2 weeks	Complete Control				
Marian et al.	2009	Case Report	38	Visual and auditory hallucinations, persecutory and paranoid delusions	Risperidone	4mg daily	6 months	Complete Control				

Katsigi-annopoulos et al.	2010	Case Report	n/a	Auditory hallucinations, delusions	Haloperidol	15mg daily	1 day	Mild Control	Amisulpride	400mg daily	4 weeks	Moderate Control (medication non-compliance)
Kobayashi et al.	2011	Case Report	64	Hallucinations, delusions	Haloperidol	6mg daily	n/a	Failure (medication non-compliance)	Chlorpromazine	In addition to haloperidol, 37.5mg daily	3-4 months	Complete Control (possible medication non-compliance)
Macedo et al.	2012	Case Report	47	Religious, paranoid, grandiose and persecutory delusions, auditory hallucinations	Haloperidol	1mg three times a day	n/a	Moderate Control (medication non-compliance)	Aripiprazole	10-15mg daily	Indefinitely	Complete Control
Muramatsu and Ahmed	2013	Case Report	45	Disorganized thought process, paranoid delusions	Aripiprazole	5mg daily	Several days	Moderate Control	Aripiprazole	5mg daily	Indefinitely	Complete Control
Ozten et al.	2013	Case Report	70	Delusional parasitosis	Haloperidol	2mg daily	10 days	Moderate Control (medication non-compliance)	Pimozide	2-4mg daily	8 weeks	Complete Control
Lee et al.	2013	Case Report	18	Persecutory delusions	Haloperidol Lorazepam	5mg daily 4mg daily	20 days	Complete Control				
Emul et al.	2013	Case Report	61	Persecutory and misidentification delusions, olfactory hallucinations, psychomotor retardation	Olanzapine	10mg daily	4 weeks	Failure	Haloperidol	2.5-7.5mg daily co-administered with olanzapine	Indefinitely	Complete Control
Dahale et al.	2014	Case Report	22	Paranoid delusions, auditory hallucinations, catatonia	Olanzapine	2.5-10mg daily	Indefinitely	Complete Control				
Oshikubo et al.	2015	Case Report	40	Disorganized thought process, paranoid delusions, auditory hallucinations	Olanzapine	10mg daily	n/a	Moderate Control				
Hazen et al.	2015	Case Report	15	Auditory hallucinations, paranoid delusions	Olanzapine Lorazepam	5mg daily 1mg every 4 hours	Several months (olanzapine)	Moderate Control				
Memon et al.	2016	Case Report	69	Hallucinations, paranoia, inappropriate affect	Haloperidol Quetiapine	n/a	n/a	Failure				
Hafner and Scholch	2017	Case Report	29	Auditory hallucinations, persecutory delusions	Olanzapine	5mg daily	41 days	Mild Control				
Urias-Urbe et al.	2017	Case Report	34	Visual and auditory hallucinations, disorganized behavior	Haloperidol	5mg IM two times a day	n/a	Failure	Risperidone Quetiapine	2mg daily 300mg daily	n/a	Failure
Ugwu et al.	2017	Case Report	16	Paranoid delusions, visual and auditory hallucinations	Haloperidol	10mg IM daily followed by 5mg PO daily	1 week 10 days	Complete Control				

mg milligram, PO per os/by mouth, IM intramuscular, n/a not available

achieve resolution of symptoms, but only the combinations of haloperidol and olanzapine and haloperidol and chlorpromazine demonstrated efficacy.

Overall, the distribution of the use of the different antipsychotics as either first or second-line agents in all cases was determined to be as follows: haloperidol (54%), chlorpromazine (25%), olanzapine (25%), risperidone (18%), aripiprazole (11%), quetiapine (7%), thioridazine (7%), trifluoperazine (4%), levomepromazine (4%) thiothixene (4%), pimozide (4%), amisulpride (4%). Additionally, the associated efficacy rates in achieving complete control of psychotic symptoms per trial of the different antipsychotics as either first or second-line agents is as follows: haloperidol (47% for n=15), chlorpromazine (29% for n=7), olanzapine (29% for n=7), risperidone (60% for n=5), aripiprazole (66% for n=3), quetiapine (0% for n=2), thioridazine (50% for n=2), trifluoperazine (100% for n=1), levomepromazine (0% for n=1) thiothixene (100% for n=1), pimozide (100% for n=1), amisulpride (0% for n=1).

DISCUSSION

It is evident from this review that the efficacy of typical and atypical antipsychotics in the treatment of hyperthyroid-related psychosis is comparable, as both classes of antipsychotics demonstrated an efficacy rate of approximately 40% as first-line agents across the existing literature. Other than agents with only one-time reported use, no antipsychotic proved to be 100% effective across the literature in completely and consistently relieving psychotic symptoms associated with hyperthyroidism. Haloperidol is the most popular choice of agent and demonstrates an equivocal efficacy rate of close to 50%, but is also the mostly likely agent to be self-discontinued by patients. Of the atypical antipsychotics, olanzapine was the most common choice, but the least efficacious of those agents used in more than 2 trials. Risperidone and aripiprazole were the next most utilized options and demonstrated relatively superior efficacy profiles of over 60%. Notably, no trials of quetiapine, amisulpride, or the typical agent, levomepromazine as first or second-line agents resulted in psychotic symptom relief. Since the effectiveness of both classes of antipsychotics is comparable, side effect profile, pre-existing medical conditions and potential drug interactions therefore comprise the main considerations when choosing an antipsychotic in psychosis secondary to hyperthyroidism. Additionally, while sample size is small (n=9 cases), multi-drug therapy consisting of either multiple antipsychotics or some combination of antipsychotics, mood stabilizers and benzodiazepines demonstrated an efficacy rate of over 66%, suggesting both that further investigation of combined therapy with greater sample size is warranted and its use should be more heavily considered in psychosis related to thyroidopathy.

Overall, our review has significant limitations. First, the small number of studies identified, all with number of subjects only ranging from one to three, makes it difficult to generalize to all patients experiencing psychosis secondary to hyperthyroidism. Second, the low-impact nature of the data, the vast majority of which comes from case reports, makes it difficult to perform any meaningful meta-analysis. Third, the heterogeneity of both the antipsychotics used and the duration of treatment throughout the literature, leaves the data presented herein somewhat difficult to interpret and furthermore, to extrapolate to one's clinical practice. Despite these limitations, however, we believe the data provides evidence for the potential benefit of antipsychotics in hyperthyroid-induced psychosis and supports the primary basis for clinician's choice of a specific antipsychotic as being side effect profile and baseline patient characteristics rather than the consideration of the pharmacology of the individual agents. We successfully applied these concepts in choosing an antipsychotic based on side-effect profile and patient-specific comorbidities to manage the psychotic symptoms in our previously described case:

Older patients who develop hyperthyroidism tend to demonstrate a paucity of the typical clinical symptoms of thyrotoxicosis such as ophthalmopathy, hyperkinesia, hypermetabolic state, hyperphagia, skin changes and heat intolerance, but do exhibit an increased incidence of weight loss and cardiovascular abnormalities (Trivalle *et al.* 1996). Only a quarter of geriatric hyperthyroid patients demonstrate typical symptoms, and this incidence has been shown to fall with age (Tibaldi *et al.* 1986). Lahey (1931) was the first to describe "apathetic thyrotoxicosis," the relatively asymptomatic presentation of hyperthyroidism in the elderly. While the pathogenesis of apathetic thyrotoxicosis is unclear, it has been suggested that age-related decreases in adrenergic tone and changes in the autonomic nervous system may be involved (Mohandas & Gupta, 2003). Additionally, animal studies have suggested that thyroid hormone transport across plasma membranes and tissue metabolism of thyroid hormone may be impaired after aging (Mooradian, 1990a; Mooradian 1990b; Mooradian & Wong, 1994). Our patient demonstrated the two symptoms most classically associated with hyperthyroidism in the elderly, weight loss and a cardiovascular anomaly in the form of systolic hypertension, but did not exemplify any other physical manifestations of hyperthyroidism, suggesting a presentation most consistent with apathetic thyrotoxicosis secondary to the imaging and laboratory-confirmed diagnosis of Graves' disease.

In addition to her overt thyroidopathy, our patient's clinical presentation was dominated by a progressive psychosis that involved paranoid delusions as well as visual and auditory hallucinations. While rare, anecdotal case reports of psychiatric manifestations of hyperthyroidism continue to be reported, and retrospective analysis has identified a diverse set of associ-

ated psychiatric symptomatology including manic, paranoid, delusional, hallucinogenic, suicidal and depressive presentations (Brownlie *et al.* 2000; Jadresic, 1990). Although a primary psychotic disorder should be considered in the differential diagnosis of an insidious, chronic psychosis, our patient's advanced age and absence of psychiatric history made the diagnosis of schizophrenia unlikely, and the presence of visual and auditory hallucinations excluded delusional disorder. Given her long-standing bilateral cataracts and near-blindness, however, a component of Charles Bonnet Syndrome may help to explain her prominent visual hallucinations, which, unlike her auditory hallucinations and paranoia, persisted through discharge. Many aspects of her visual hallucinations, including their transient nature, the element of photopsia, her lack of fear towards the visions, and in particular (after some days of antipsychotic treatment), her insight that her hallucinations were not real, are consistent with Charles Bonnet Syndrome (Pang, 2016). However, this diagnosis of exclusion could not be accurately made while her treatment for psychosis was ongoing (Kester, 2009).

In an elderly patient, psychosis superimposed on underlying neurocognitive disorder also must be considered in the differential, however, the patient demonstrated intact executive functioning based on MoCA exam, had benign head imaging, and showed no evidence of a movement or gait abnormality that one may expect in neurodegenerative diseases associated with psychosis such as Lewy Body Dementia (LBD). Additionally, the intransient nature of her symptoms coupled with a negative infectious workup essentially excluded delirium as well. Furthermore, malnutrition alone was thought not to be a primary etiology of our patient's progressive dementia or psychosis given that the most commonly associated nutritional deficiencies were ruled out—namely vitamin B12 deficiency and poor calcium homeostasis, which would potentially be reflective of parathyroid pathology or vitamin D deficiency (Lachner *et al.* 2012; Boerman *et al.* 2016; Amaral *et al.* 2016). Given, however, that the patient presented after two years of living in an incapacitating neuropsychiatric state seemingly without outside contact, a more insidious neurological and systemic insult secondary to chronically poor nutritional status could not be totally excluded.

In our elderly patient, we chose an atypical antipsychotic for the management of her psychosis in order to best avoid the introduction of a confounding iatrogenic movement disorder that is more likely to manifest after the administration of typical antipsychotics in the form of extrapyramidal symptoms (EPS) (Gao *et al.* 2008). EPS would create a parkinsonian-type picture and force the reconsideration of a neurodegenerative illness, such as LBD, as the fundamental cause for the psychosis. A case-controlled study of 3,512 Medicaid patients over age 65 revealed that those who had received an antipsychotic medication in the preceding 90 days were

5.4 times more likely to consequently receive an anti-Parkinson's medication due to the well-described "prescribing cascade" phenomenon (in which a new drug is prescribed to treat symptoms from an unrecognized adverse drug effect related to an existing therapy) (Avorn *et al.* 1995; Rochon & Gurwitz, 1997).

Of the atypical antipsychotics, risperidone was chosen both based on its suggested enhanced efficacy profile relative to other antipsychotics in hyperthyroid-related psychosis and also by a process of elimination: Given that hyperthyroidism is inherently associated with cardiovascular destabilization, ziprasidone, which is the most likely of the atypicals to prolong the QT interval and cause arrhythmia, was not considered (Geodon Ziprasidone HCl [package insert], 2010). Additionally, there is no evidence of its utility in hyperthyroid-induced psychosis. In contrast to ziprasidone, a couple of authors have favored aripiprazole for its reported lack of association with QT prolongation and torsade de pointes arrhythmia (Macedo *et al.* 2012; Muramatsu & Ahmed, 2013; Wenzel-Seifert *et al.* 2011). However, aripiprazole has been shown to cause significant weight loss in geriatric inpatients relative to other atypicals, and therefore would not be a good choice in this elderly, cachectic patient (Yeung *et al.* 2017). Many, but not all, of the antipsychotics have anti-cholinergic activity that can cause blurred vision, constipation, dry mouth, impotence, urinary retention and, most critically, cognitive impairments and delirium (Sadock & Sadock, 2005). Compared with younger patients, older patients have insufficiencies in drug metabolism and age-related deficits in cholinergic transmission that make them more susceptible to the anticholinergic profiles of the various antipsychotics (Feinberg, 1993). Not only have associations been found between anticholinergic medications and the acquisition of community-acquired pneumonia in the elderly, but multiple studies have also shown that persons over age 65 taking medications with high anti-cholinergic activity have an increased risk for cognitive decline and dementia (Carrière *et al.* 2009; Gray *et al.* 2015; Paul *et al.* 2015). A study measuring the anti-cholinergic activity of over 100 medications commonly used in older adults revealed that clozapine, olanzapine and chlorpromazine were among the most anticholinergic medications (Chew *et al.* 2008). Furthermore, in a head-to-head comparison using SPECT imaging, olanzapine was shown to have significantly higher muscarinic receptor occupancy in the human striatum and cortex than risperidone, favoring the choice of risperidone in our elderly patient (Lavalaye *et al.* 2001). Lastly, neither quetiapine nor amisulpride were considered since there is no evidence of its successful use in this setting.

CONCLUSIONS

In conclusion, risperidone proved efficacious for the attenuation of psychotic symptoms secondary to Graves' disease and was well-tolerated in an elderly patient. Additionally, a systematic review of the literature has revealed that typical and atypical antipsychotics are anecdotally equally effective in the treatment of hyperthyroid-related psychosis. However, risperidone, which is suggested along with aripiprazole to be one of the more efficacious atypical antipsychotics, may be the best choice of the previously trialed antipsychotics for elderly, cachectic patients presenting with a clinical picture of apathetic thyrotoxicosis. Nevertheless, given the limited amount of existing evidence sourced only from case reports and case series, further, higher powered studies are needed to determine the generalizability of the use of risperidone for the management of psychosis in thyrotopathy.

ACKNOWLEDGMENTS

Victoria Dinsell, MD, Department of Psychiatry, NYU School of Medicine

Steven Liu, MD, Department of Medicine, NYU School of Medicine

Alex Yanai, BS, NYU Health Sciences Library, NYU School of Medicine

Wilson Chung, MD, Department of Psychiatry, NYU School of Medicine

Zoe Blacksin, MD, Department of Psychiatry, NYU School of Medicine

Caroline Katzman, BA, NYU School of Medicine Psychiatry Consult Liaison Faculty at Bellevue Hospital Center, NYU School of Medicine

FINANCIAL DISCLOSURE

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

REFERENCES

- Amaral AD, Novais C, Coelho MA, Silva A, Curral R, Brandao I, et al (2016). Organic psychosis due to hypoparathyroidism in an older adult: a case report. *Rev Bras Psiquiatr.* **38**: 349–350.
- Avorn J, Bohn RL, Mogun H, Gurwitz JH, Monane M, Everitt D, et al (1995). Antipsychotic drug exposure and treatment of parkinsonism in the elderly: a case-control study. *Am J Med.* **99**: 48.
- Bianco FJ, Lerro FA (1972). Schizophrenic syndrome, thyrotoxicosis and haloperidol. *Psychosomatics.* **13**: 120–121.
- Boerman R, Cohen D, Schulte PF, Nugter A (2016). Prevalence of Vitamin D deficiency in Adult Outpatients With Bipolar Disorder or Schizophrenia. *J Clin Psychopharmacol.* **36**: 588–592.
- Brownlie BE, Rae AM, Walshe JW, Wells JE (2000). Psychoses associated with thyrotoxicosis – 'thyrotoxic psychosis.' A report of 18 cases, with statistical analysis of incidence. *Eur J Endocrinol.* **142**: 438–444.
- Bunevicius R, Prange Jr AJ (2006). Psychiatric manifestations of Graves' hyperthyroidism: pathophysiology and treatment options. *CNS Drugs.* **20**: 897–909.
- Bursten B (1961). Psychoses associated with thyrotoxicosis. *Arch Gen Psychiatry.* **4**: 267–273.
- Carrière I, Fourrier-Reglat A, Dartigues JF, Rouaud O, Pasquier F, Ritchie K, et al (2009). Drugs with anticholinergic properties, cognitive decline, and dementia in an elderly general population: the 3-city study. *Med.* **169**: 1317.
- Caudill TG, Lardinois CK (1991). Severe thyrotoxicosis presenting as acute psychosis. *West J Med.* **155**: 292–293.
- Chew ML, Mulsant BH, Pollock BG, Lehman ME, Greenspan A, Mahmoud RA (2008). Anticholinergic activity of 107 medications commonly used by older adults. *J Am Geriatr Soc.* **56**: 1333.
- Cooper GS, Stroehla BC. The epidemiology of autoimmune diseases (2003). *Autoimmun Rev.* **2**: 119–125.
- Corn TH, Checkley SA (1983). A case of recurrent mania with recurrent hyperthyroidism. *BJP.* **143**: 74–76.
- da Silva JA, Almeida JT, Corrêa BB, Narigão M, Xavier M (2009). Acute psychotic episode in a patient with thyrotoxicosis factitia. *BMJ Case Rep.* 2009:bcr08.2008.0676.
- Dahale AB, Chandra PS, Thippeswamy H, Desai G, Reddy D (2014). Postpartum psychosis in a woman with Graves' disease: a case report. *Gen Hosp Psychiatry.* **36**: 761.e7–8.
- Emul M, Sakalli A, Erol TC, Ertan T (2013). Thyrotoxic psychosis in an elderly woman and haloperidol use: a case report. *Psychogeriatrics.* **13**: 49–51.
- Feinberg M (1993). The problems of anticholinergic adverse effects in older patients. *Drugs Aging.* **3**: 335–348.
- Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D, et al (2013). The CARE guidelines: consensus-based clinical case reporting guideline document. *J Med Case Rep.* **7**: 223.
- Gao K, Kemp DE, Ganocy SJ, Gajwani P, Xia G, Calabrese JR (2008). Antipsychotic-induced extrapyramidal side effects in bipolar disorder and schizophrenia: a systematic review. *J Clin Psychopharmacol.* **28**: 203.
- Geodon Ziprasidone HCL [package insert] (2010). New York, NY: Roerig Division of Pfizer Inc.
- Gray SL, Anderson ML, Dublin S, Hanlon JT, Hubbard R, Walker R et al (2015). Cumulative use of strong anticholinergics and incident dementia. *JAMA Intern Med.* **175**: 401–417.
- Greer S, Parsons V (1968). Schizophrenia-like psychosis in thyroid crisis. *BJP.* **114**: 1357–1362.
- Hafner S, Scholch D (2017). Graves' disease and psychosis in a young woman: pathophysiologic considerations. *Prim Care Companion CNS Disord.* **19**: 16102081.
- Hazen EP, Sherry NA, Parangi S, Rabito CA, Sadow PM (2015). Case 10-2015: a 15-year-old girl with Graves' disease and psychotic symptoms. *N Engl J Med.* **372**: 1250–1258.
- Jadresic DP (1990). Psychiatric aspects of hyperthyroidism. *J Psychosom Res.* **34**: 603–615.
- Katsigiannopoulos K, Georgiadou E, Pazarlis P, Karastergiou A, Papazisis G, Bozikas V, et al (2010). Psychotic disorder as a manifestation of Graves' disease. *Psychosomatics.* **51**: 449–450.
- Kester EM (2009). Charles Bonnet syndrome: case presentation and literature review. *Optometry.* **80**: 360–366.
- Kobayashi N, Tajiri J, Takano M (2011). Transient psychosis due to painless thyroiditis in a patient with anxiety disorder: a case report. *J Med Case Rep.* **5**: 534.
- Lachner C, Steinle NI, Regenold WT (2012). The Neuropsychiatry of Vitamin B12 Deficiency in Elderly Patients. *J Neuropsychiatry Clin Neurosci.* **24**: 5–15.
- Lahey FH (1931). Non-activated (apathetic) type of hyperthyroidism. *N Engl J Med.* **204**: 747–748.
- Lavalaye J, Booij J, Linszen DH, Reneman L, van Royen EA (2001). Higher occupancy of muscarinic receptors by olanzapine than risperidone in patients with schizophrenia. A [123I]-IDEX SPECT study. *Psychopharmacology.* **156**: 53–57.
- Lee KA, Park KT, Yu HM, Jin HY, Baek HS, Park TS (2013). Subacute thyroiditis presenting as acute psychosis: a case report and literature review. *Korean J Intern Med.* **28**: 242–246.

- 32 Macedo LR, Marino J, Bradshaw B, Henry, J (2012). Graves' hyperthyroidism-induced psychosis treated with aripiprazole—a case report. *J Pharm Pract.* **26**: 59–61.
- 33 Mahmood A, Ashton AK, Hina FH (2005). Psychotic symptoms with underlying Graves' disease: a case report. *Prim Care Companion J Clin Psychiatry.* **7**: 311–312.
- 34 Marian G, Nica EA, Ionescu BE, Ghinea D (2009). Hyperthyroidism—cause of depression and psychosis: a case report. *J Med Life.* **2**: 440–442.
- 35 Memon R, Fan W, Snyder R, Krishnamurthy M (2016). Thyroid storm presenting as psychosis: masked by diabetic ketoacidosis. *J Community Hosp Intern Med Perspect.* **6**: 31750.
- 36 Mohandas R, Gupta KL (2003). Managing thyroid dysfunction in the elderly. Answers to seven common questions. *Postgrad Med.* **113**: 54–68.
- 37 Moher D, Liberati A, Tezloff J, Altman DG, The PRISMA Group (2010). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Intl J of Surgery.* **8**: 336–341.
- 38 Mooradian AD (1990a). Blood-brain transport of triiodothyronine is reduced in aged rats. *Mech Ageing Dev.* **52**: 141–147.
- 39 Mooradian AD (1990b). The hepatic transcellular transport of 3, 5, 3' – triiodothyronine is reduced in aged rats. *Biochim Biophys Acta.* **1054**: 1–7.
- 40 Mooradian AD, Wong NC (1994). Age-related changes in thyroid hormone action. *Eur J Endocrinol.* **131**: 451–461.
- 41 Muramatsu RS, Ahmed I (2013). Comments on graves' hyperthyroidism-induced psychosis treated with aripiprazole: a case report. *J Pharm Pract.* **26**: 460–461.
- 42 Nibuya M, Sugiyama H, Shioda K, Nakamura K, Nishijima K (2002). ECT for the treatment of psychiatric symptoms in Basedow's disease. *J ECT.* **18**: 54–57.
- 43 Oshikubo G, Tochigi M, Akahane A, Hayashi N, Ikebuchi E (2015). Graves' hyperthyroidism-induced psychosis in a patient with periventricular nodular heterotopia. *Psychiatry Clin Neurosci.* **69**: 505–506.
- 44 Ozten E, Tufan A, Cerit C, Sayar G, Ulubil I (2013). Delusional parasitosis with hyperthyroidism in an elderly woman: a case report. *J Med Case Rep.* **7**: 17.
- 45 Pang L (2016). Hallucinations Experienced by Visually Impaired: Charles Bonnet Syndrome. *Optom Vis Sci.* **93**: 1466–1478.
- 46 Paul KJ, Walker RL, Dublin S (2015). Anticholinergic medications and risk of community-acquired pneumonia in elderly adults: a population-based case-control study. *J Am Geriatr Soc.* **63**: 476–485.
- 47 Rochon PA, Gurwitz JH (1997). Optimising drug treatment for elderly people: the prescribing cascade. *BMJ.* **315**: 1096.
- 48 Sadock BJ, Sadock VA (2005). Kaplan and Sadock's Comprehensive Textbook of Psychiatry, vol. 1 and 2. 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins.
- 49 Singh J, Gupta N (2007). Association of psychosis and hyperthyroid goiter: a case report. *Prim Care Companion J Clin Psychiatry.* **9**: 154–155.
- 50 Snabboon T, Khemkha A, Chaiyaumporn C, Lalitanantpong D, Sridama V (2009). Psychosis as the first presentation of hyperthyroidism. *Intern Emerg Med.* **4**: 359–360.
- 51 Tibaldi JM, Barzel US, Albin J, Surks M (1986). Thyrotoxicosis in the very old. *Am J Med.* **81**: 619–622.
- 52 Trivalle C, Doucet J, Chassagne P, Landrin I, Kadri N, Menard JF, et al (1996). Differences in the signs and symptoms of hyperthyroidism in older and younger patients. *J Am Geriatr Soc.* **44**: 50–53.
- 53 Ugwu ET, Maluze J, Onyebueke GC (2017). Graves' thyrotoxicosis presenting as schizophreniform psychosis: a case report and literature review. *Int J Endocrinol Metab.* **15**: e41977.
- 54 Urias-Uribe L, Valdez-Solis E, González-Milán C, Ramírez-Rentería C, Ferreira-Hermosillo A (2017). Psychosis crisis associated with thyrotoxicosis due to Graves' disease. *Case Reports in Psychiatry.* 2017:6803682.
- 55 Wenzel-Seifert K, Wittmann M, Haen E (2011). QTc prolongation by psychotropic drugs and the risk of torsade de pointes. *Dtsch Arztebl Int.* **108**: 687–693.
- 56 Yang SJ, Wang SY, Chen CC (2003). Acute psychotic state due to hyperthyroidism following excision of a mandible bone tumor: a case report. *Kaohsiung J Med Sci.* **19**: 29–32.
- 57 Yeung EYH, Chun S, Douglass A, Lau TE (2017). Effect of atypical antipsychotics on body weight in geriatric psychiatric inpatients. *SAGE Open Medicine.* **5**: 1–8.

SUPPLEMENTARY APPENDIX A:

PubMed Database Sample Search Strategy

1. Hyperthyroidism [MeSH Terms]
2. "Hyperthyroidism"
3. "Hyperthyroid"
4. Graves Disease [MeSH Terms]
5. "Graves Disease"
6. "Graves"
7. Thyrotoxicosis [MeSH Terms]
8. "Thyrotoxicosis"
9. "Thyrotoxic"
10. Thyroid Crisis [MeSH Terms]
11. "Thyroid Crisis"
12. "Thyrotoxic Crisis"
13. Psychotic Disorders [MeSH Terms]
14. "Psychotic Disorders"
15. "Psychotic Symptoms"
16. "Psychosis"
17. "Psychotic"
18. Delusions [MeSH Terms]
19. "Delusions"
20. "Delusional"
21. Hallucinations [MeSH Terms]
22. "Hallucinations"
23. Antipsychotic Agents [MeSH Terms]
24. "Antipsychotic Agents"
25. "Antipsychotic"
26. "Neuroleptic"
27. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12
28. 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22
29. 23 OR 24 OR 25 OR 26
30. 27 AND 28
31. 27 AND 29
32. 30 OR 31

SUPPLEMENTARY APPENDIX A:

PRISMA Checklist

TITLE

1. *Title:* Antipsychotics in Hyperthyroid-Related Psychosis: Case Report and Systematic Review

ABSTRACT

2. *Abstract/Structured Summary:* Please see **Abstract** in manuscript text.

INTRODUCTION

3. *Rationale:* Please see **Section 1 (Introduction)** in manuscript text.
4. *Objectives:* Please see **Section 2.1** in manuscript text for specific search question. Please see **Section 2.1** in manuscript text for definitions of primary and secondary outcomes.

METHODS

5. *Protocol:* Please see **Section 2 (Methods)** in manuscript text for further information on protocol used for review.
6. *Eligibility Criteria:* Please see **Section 2.1** in manuscript text for details on inclusion and exclusion criteria. All relevant publications were included (all-inclusive review performed) because on cursory initial review by primary author it was determined that there was a relative paucity of relevant literature.
7. *Information Sources:* Please see **References** for a list of the literature analyzed in review. These publications were found via search strategy defined in **Section 2.1** in PubMed, Ovid MEDLINE and PMC databases. Literature included publications from 1960 to 2017. Last date searched was 11/05/17.
8. *Search:* See **Supplementary Appendix A** for example of search strategy used in PubMed and then tailored for Ovid MEDLINE and PMC databases.
9. *Study Selection:* Please see **Section 2.2** in manuscript text for details on study selection process.
10. *Data Collection:* Please see **Section 2.3** in manuscript text for explanation of methods of data extraction.
11. *Data items:* Please see **Section 2.3** in manuscript text for delineation of data fields included.
12. *Risk of Bias:* Please see **Section 2.3** in manuscript text for quality assessment methodology performed at the study level.
13. *Summary Measures:* Principal summary measures included analyzing the percentage of studies reviewed that used a given class of and a given antipsychotic, and additionally, to measure efficacy, the percentages of studies that used a specific class of antipsychotic (and a specific antipsychotic) and also demonstrated *complete control* of psychotic symptoms as defined in primary outcome methodology (see **Section 2.1** in manuscript text).
14. *Synthesis of Results:* No quantitative meta-analysis was performed beyond what is described in (13) given the heterogeneity of the limited data extracted.
15. *Risk of Bias Across Studies:* Case reports and case series may selectively report outcomes such as symptom improvement. Additionally, overall publication bias in case studies and case series generally is publication of good outcomes (poor outcomes less frequently published).
16. *Additional Analyses:* No additional analysis was performed.

RESULTS

17. *Study Selection:* Please see **Section 4 (Results)** in manuscript text for details on numbers of studies screened and numbers of studies included in review. Flow diagram of selection process can be seen in **Section 4, Figure 1**.
18. *Study Characteristics:* See **Table 1, referenced in Section 4 (Results)** for study characteristics of all included literature and extracted data.
19. *Risk of Bias Within Studies:* As described in **Section 2.3** of manuscript text, all included studies were evaluated for risk of bias based on fitting of at least 70% of criteria delineated in the CARE guidelines (see **References**) for reporting case studies.

20. *Results of Individual Studies*: Please see **Section 4 (Results)** for discussion of results of individual studies, quantitative and qualitative assessment and **Table 1** for summary of data for each study including specific intervention(s).
21. *Synthesis of Results*: N/A, no quantitative meta-analysis was performed.
22. *Risk of Bias Across Studies*: Please see items **15** and **19**.
23. *Additional Analysis*: No additional analysis was performed.

DISCUSSION

24. *Summary of Evidence*: Please see **Section 5 (Discussion)** in manuscript text for summarization of main findings of systematic review and relevance to health care providers.
25. *Limitations*: Please see **Section 5 (Discussion)** in manuscript text for a thorough discussion of the limitations of our review.
26. *Conclusions*: Please see **Section 6 (Conclusions)** in manuscript text.
27. *Funding*: Please see **Title Page (page 1)** for description of funding and support for research.