Canadian Geriatrics Society

PHARMACOLOGICAL MANAGEMENT OF INAPPROPRIATE SEXUAL BEHAVIOURS IN PATIENTS WITH DEMENTIA RESIDING IN LONG-TERM CARE: REVIEW OF THE EVIDENCE

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Abstract

Inappropriate sexual behaviours (ISB) are an infrequent but challenging form of behavioural and psychological symptom of dementia (BPSD), particularly in the long-term care context, where shared living spaces put other residents at risk of assault. Behavioural interventions are recommended as first-line therapy, but often patients living in long-term care exhibiting ISB will require pharmacological therapy. To review the evidence for treating ISB pharmacologically within the long-term care context, a scoping review was performed. MEDLINE, EMBASE, and CINAHL were searched for literature related to dementia, long-term care, and sexual behaviour. Twenty-eight articles were included, reviewing antidepressants, antipsychotics, anticonvulsants, mood stabilizers, and hormonal agents. The available evidence is sparse, the bulk of which is from case reports of male patients. The use of any medication to treat ISB is off-label and not well studied, therefore caution should be used when initiating pharmacotherapy for this indication.

This article has been peer reviewed.

Conflict of Interest: None

This article was published in May 2023

Key words:
dementia, long-term care, inappropriate sexual behaviours

Key Points

When considering the management of inappropriate sexual behaviour (ISB) in patients with dementia residing in long-term care:

- Consider the context of the behaviour, as well as risk to staff and other residents
- Non-pharmacological behavioural interventions remain first-line, but pharmacological therapy is often necessary
- All medications used for ISB are employed off-label
- Medication classes used to treat ISB include antidepressants (SSRI, serotonin modulators, tricyclic antidepressants), antipsychotics (mostly atypical), anticonvulsants, mood stabilizers, and hormonal agents (including antiandrogens and estrogen)
- Consider dual indications for medications when deciding which agent to start

Introduction

According to the Canadian Institute for Health Information, 69% of residents in long-term care have a diagnosis of dementia. Of these individuals, 40% have severe cognitive impairment and 50% have behaviours and psychological symptoms of dementia (BPSD)[1]. Inappropriate sexual behaviour (ISB) is a particularly challenging form of BPSD. ISB presents a complex challenge for residents, their families, and staff in long-term care facilities, even though it is a less common presentation of BPSD. Unfortunately, the pharmacological management of ISB is poorly researched.

Reported frequency of ISB in those with dementia is variable, ranging from 1.8% to 25%, but is generally more common for males, in long-term care homes, and in those with severe dementia[2–4]. For vulnerable residents living in long-term care, ISB may result in high-risk situations for all involved. Many residents in long-term care may be unable to consent, refuse touch, call for help, or physically protect themselves from unwanted physical advances of their co-residents[5].

In considering the treatment of ISB, it may be helpful to consider its' potential pathophysiology. The causes of ISB are not well established. The frontal lobes, limbic system, hypothalamus, and striatum are often affected in major neurocognitive disorders and play a role in sexual drive and behaviour regulation[6,7]. The resident's previous personality characteristics and baseline need for intimacy combined with the confusion, disinhibition, and worsening judgement that often accompany major neurocognitive disorders can contribute[8]. One should always first consider acute and reversible causes with a new presentation of ISB, including delirium, medication side effect (particularly dopaminergic agents), mania, psychosis, substance use, and postictal confusion[8,9].

Most treatment approaches to ISB described in the literature appropriately start with non-pharmacological behavioural intervention. However, given the inability to constantly supervise residents living in shared spaces and the vulnerability of other residents with cognitive and functional impairments, many patients in long-term care are treated pharmacologically. There are no randomized controlled trials of medications for ISB. Instead, pharmacological agents with the side effect of reducing libido are used off-label to control ISB, including antidepressants, antipsychotics, antiseizure medications, and antiandrogens[4]. Most studies have been cohort or case studies. Given the limitations of the research, a scoping review was chosen to address this research question.

Methods

MEDLINE, EMBASE and CINAHL were used for this scoping review. All primary literature relevant to the three dimensions of interest for this topic (dementia, long-term care or institutionalized elsewhere, and inappropri-

ate sexual behaviour) were considered eligible. Each included article had to be published in or translated to English. No limitations were set for date of publication. A single reviewer performed a title screen, an abstract screen, then full text review.

Results

When generating the search terms, the decision was made to include "sex" as a key word. This greatly increased the number of articles generated from the search as it retrieved literature that stratified patients based on gender, rather than focusing on ISB. However, comparing the datasets with and without "sex" as a search term showed many articles that would have been missed by excluding this important variable. The search gathered a total of 4315 articles, 48 of which, based on title screen and/or abstract review, were potentially relevant to ISB and went on to full text review. Citations were pulled from a number of reviews and were included in the study if they met the pre-specified eligibility criteria. After full-text review, 28 articles were included in the following review. Results are summarized in Table 1.

Antidepressants

Antidepressants have been used to treat ISB due to their effects on libido and treatment of paraphilias[7]. Furthermore, they can be leveraged for a dual indication, such as irritability, depression, or apathy, common symptoms in dementia[10]. Most are generally considered safe or low risk in older adults[10]. From the studies collected, the most frequently used antidepressant was the selective serotonin reuptake inhibitor (SSRI) citalopram. Citalopram was reviewed in a case study of a single patient and a retrospective chart review with seven patients. In these eight cases, citalopram led to resolution of symptoms in one individual, a partial response in three, no response in three, and worsening of symptoms in one[5,7]. The patient who responded completely to citalopram was treated as monotherapy with resolution of behaviour[7]. The three patients that had a partial response were treated concurrently with olanzapine, risperidone, or a combination of olanzapine and medroxyprogesterone acetate (MPA)[5]. The only other SSRI studied was paroxetine, which lead to resolution of symptoms when used as monotherapy in two patients[11,12]. Other antidepressants used included the serotonin modulators mirtazapine and trazodone. In one patient, mirtazapine led to partial response when used in combination with citalopram and olanzapine. In another case, trazodone resulted in resolution of symptoms when used with risperidone and MPA[5,8]. Finally, clomipramine, an old tricyclic antidepressant, was used as monotherapy in two patients with resolution of symptoms[13]. It is worth noting that the studies using clomipramine and paroxetine were published in 1995 and 1997 respectively. The use of these medications in older adults have fallen out of favour due to their anticholinergic side effects and risk of delirium[10].

Antipsychotics

The use of antipsychotics in patients with dementia is generally not recommended due to the increased risk of mortality in this population, but they are often used with caution in patients with BPSD[10]. Antipsychotics have been postulated to be effective in reducing ISB due to their dopamine-blocking activity[14]. Aripiprazole was found to be effective in two cases studies, one female with Alzheimer's disease and one male with frontotemporal dementia[15,16]. A review of 10 patients looked at olanzapine, quetiapine, and risperidone alone or in combination with other medications in the management of ISB. Olanzapine was used in six patients in combination with other medications and found to be only partially effective. Of these cases, three patients used olanzapine with citalopram, one patient used it with both citalopram and mirtazapine, and another used olanzapine with citalopram and MPA[5]. Quetiapine was used as monotherapy in one patient, but failed to produce any response[5]. In the same study, risperidone was used for three patients, producing a partial response in only one patient when used in combination with citalopram[5]. In another case report, one patient responded favourably to risperidone in combination with trazodone and oral MPA therapy[8].

In the largest study found, risperidone and haloperidol were compared with respect to their efficacy in controlling BPSD in a double blind randomized cross-over study. The study involved 114 patients in long-term care with clinically significant BPSD on the Behavioural Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) and Cohen-Mansfield Agitation Inventory (CMAI) scales. In this study, physical sexual advances were included as measured on the CMAI scale. The study did not report how many of the 114 patients had

ISB at baseline. At mean doses of risperidone 0.8mg and haloperidol 0.83mg, risperidone was found to be more effective in reducing physical sexual advances when compared to haloperidol. In this study, six patients stopped the trial due to somnolence (haloperidol), nausea (risperidone), and seizure (not felt to be drug related)[17].

Anticonvulsants

Gabapentin and carbamazepine have been used in cases of ISB, but the mechanisms are poorly understood. Gabapentin may result in decreased libido, erectile dysfunction, and difficulty with orgasm [4]. Carbamazepine has been shown to reduce testosterone levels in women[4]. However, side effects of these medications include dizziness, drowsiness, ataxia, confusion, and falls which are problematic in older adults[18,19]. In case reports, gabapentin was used in one patient who failed to respond to citalopram for ISB. In this case, there was improvement in ISB after four weeks of monotherapy[20]. Two other case reports found efficacy with low dose gabapentin. In one case, it was used in conjunction with quetiapine, which was eventually weaned and discontinued[21]. In another case report, carbamazepine was used in a patient who failed to respond to paroxetine. After achieving a therapeutic serum concentration, the ISB resolved[22].

Mood stabilizers

Mood stabilizers were rarely encountered in this scoping review. However, one case study used lithium in an older patient with a history of bipolar disorder with mania. In this case, lithium was used in combination with olanzapine. Treatment resulted in a partial response[5].

Hormonal therapy

The highest number of studies collected in this review examined hormonal therapy for control of ISB. In total, 11 studies were reviewed examining 43 patients. Pharmacologic management with medroxyprogesterone acetate (MPA), cyproterone acetate (CPA), leuprolide, and estrogen are theoretically effective for ISB as they reduce levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) at the level of the pituitary, ultimately decreasing the serum testosterone level[4,14]. Finasteride is an alpha-5-reductase inhibitor that blocks the peripheral conversion of testosterone to dihydrotestosterone. While often used to treat benign prostate hyperplasia, the hormonal side effects commonly result in erectile dysfunction and decreased libido[23]. However, hormonal agents have significant side effects involving most major body systems. These are detailed below.

Medroxyprogesterone acetate

Medroxyprogesterone acetate (MPA) can be given orally or intramuscularly. The use of MPA should be avoided in patients with active or previous thromboembolic disease, including deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke, and retinal vascular disease. MPA may also exacerbate hormone dependent cancers, including prostate cancers. Other side effects include osteoporosis, liver disease, adrenal suppression, depression, edema, diabetes, weight loss or gain[24]. Several case reports have shown MPA to be effective in ISB as monotherapy or in combination therapy[5,25–28]. Only one case used oral MPA, which was successful in controlling ISB when used with trazodone and risperidone[8]. The remaining studies used intramuscular MPA.

One case report described a patient who required admission to geriatric inpatient care for troublesome ISB, including sexual assault and sexual advances towards young family members. The patient had been previously treated with benzodiazepines, antipsychotics, antidepressants, and anticonvulsants with poor control of his symptoms. Once titrated to an effective dose, intramuscular MPA produced and maintained control of his ISB to the point where he could be discharged and maintained in the community[26]. Another case report described a male patient who received MPA after failing thioridazine. His behaviours resolved and he was successfully weaned off his antipsychotic[27]. Another male had failed combination therapy with antipsychotics, antidepressants, and mood stabilizers for his ISB, although the details of these therapies were not provided. He was then started on MPA and his ISB resolved within 10 injections[28].

Another case series described five patients living in either long-term care or a geriatric inpatient unit receiving MPA intramuscularly. All patients had been treated with antidepressants, antipsychotics, anticonvulsants, and/or anxiolytics for their ISB first and failed to respond adequately. In all cases, the ISB resolved once the dose of MPA was properly titrated[25]. Finally, Bardell et al reviewed five patients receiving MPA, either alone or in combination with either citalopram, olanzapine, or leuprolide. All five patients had partial response to the therapy[5].

Of note, the above was the only case in which leuprolide was encountered in this review. Leuprolide is a gonadotrophin-releasing hormone agonist, which is typically used in the management of certain hormone sensitive cancers, but is also used for males with problematic paraphilias. Leuprolide may result in thromboembolic events, prolong QT, seizures, pituitary apoplexy, and mania. It should be used cautiously and with close monitoring[29].

Cyproterone acetate

Cyproterone acetate (CPA) is a synthetic progesterone derivative with risks similar to those of MPA. The use of CPA should be avoided in patients with active or previous thromboembolic disease. Furthermore, there is a black box warning in Canada due to its' hepatoxicity[30]. One paper reviewed the use of CPA in two male patients admitted to a geriatric inpatient unit for difficult to control ISB. The first patient had a history of bipolar disorder which was managed with valproate, olanzapine, lithium, lorazepam, and L-DOPA. The authors noted that mania was not felt to be contributing to ISB, but did not mention the possible role of L-DOPA in exacerbating ISB. The patient was started on CPA with resolution of his ISB within a few days. The second patient had ISB despite trials of valproate, mirtazapine, and risperidone. He experienced resolution of his ISB within a few days of starting CPA[31].

Estrogen

Estrogen has been used in men and women to try to decrease aggression and ISB, in the forms of conjugated estrogen and diethylstilbestrol. The use of conjugated estrogen is associated with venous thromboembolic disease, dyslipidemia, breast cancer, as well as endometrial hyperplasia when used without progesterone in women with a uterus[32]. Diethylstilbestrol is no longer routinely prescribed. Conjugated estrogen was used in a 4-week randomized double blind placebo-controlled study with 14 participants. Eight of the patients received conjugated estrogen therapy titrating up to a dose of 2.5mg daily over the course of four weeks. When compared to the placebo group, there was no significant improvement in sexually aggressive behaviours, but total aggression scores were significantly lower in the estrogen group[33]. A case study reviewed a patient who was started on conjugated estrogen after failing haloperidol, risperidone, and lorazepam for ISB. With therapy, sexual aggression improved 80%, and sexual comments improved 55% as per staff observation, nursing reports, and progress notes[34]. Finally, a patient was treated with diethylstilbestrol as monotherapy with resolution of his ISB[35].

Finasteride

One study reviewed 11 male patients with known benign prostatic hyperplasia and vascular dementia with ISB. All patients were treated with finasteride for 12 weeks. In 6 of these patients, ISB resolved within 8 weeks. The other 5 patients required combination therapy: one with propranolol, two with propranolol and quetiapine, one with oxycarbamazepine, and one required gonadotropin-releasing hormone agonist for intractable ISB[36]. The mechanisms by which antipsychotics and anticonvulsants control ISB were discussed previously. Beta-blockers are thought to decrease libido by blunting adrenergic drive[4].

Antihistamines

Cimetidine is an antihistamine that has been shown to have non-hormonal antiandrogen activity, however it is not favoured in older adults due to its relatively high anticholinergic burden and subsequent risk of delirium[37]. Two studies reviewed cimetidine. One case report reviewed a patient who had resolution of ISB with cimetidine after failing to respond to memantine[3]. The other study was a retrospective chart review that found a subset of 20 patients with dementia and ISB treated with non-hormonal antiandrogen therapies, in-

cluding cimetidine, ketoconazole, and spironolactone. Patients were given cimetidine initially as monotherapy and increased to either an effective dose or the point of adverse effects (nausea, arthralgia, and headache). Fourteen of 20 patients responded to cimetidine alone. The remaining six patients required ketoconazole and/or spironolactone with resolution of their ISB[37]. While ketoconazole is an antifungal and spironolactone is a potassium-sparing diuretic, they both have non-hormonal antiandrogen activity which may decrease libido. No other details were given about those six patients.

Cholinesterase inhibitors

Cholinesterase inhibitors are often used in the management of BPSD, in addition to their function for cognitive stabilization in those with major neurocognitive disorder[14]. However, they have not been shown to be effective in managing ISB within the long-term care context. Moreover, there are a handful of case reports attributing onset of ISB with initiation of cholinesterase inhibitors as these medications can be stimulating.

Discussion

There have been several reviews published on the pharmacological treatment of ISB in dementia[4, 14, 23], but this is the first review of this topic in the context of patients living in long-term care. It is important to focus on this context due to safety concerns for other residents sharing accommodations who may be more vulnerable to assault due to their own cognitive and functional impairments. Unfortunately, the evidence supporting pharmacological management of ISB is sparse and of very poor quality.

If it has been determined that ISB is high-risk, and not responding to behavioural interventions, then a pharmacological approach can be tried. As demonstrated in this review, the evidence for pharmacotherapy is weak. With this understanding, it would be reasonable to choose an antidepressant as first-line therapy for ISB. Sertraline, citalopram, or escitalopram are excellent options given their safety profile in older adults with cognitive impairment. Another reasonable first or second-line agent for men with symptomatic BPH would be an alpha-5-reductase inhibitor, such as finasteride or dutasteride. Gabapentin could be considered as a second-line agent, particularly at low doses of 100mg twice or three times daily. However, this should be done with caution as gabapentin can cause dizziness, drowsiness, ataxia, confusion, and falls, particularly when used in combination with other sedating medications, such as opioids. Furthermore, there may be a role for cimetidine as a second-line agent, but this medication should be used with caution as it is known to have anticholinergic side effects which can cause delirium.

These suggested therapies can take several weeks to become effective, which may not be a suitable timeline in more urgent cases. If a response is required within a few days, antipsychotic medications may have a role. Risperidone, olanzapine, or aripiprazole would be reasonable options if QTc is not prolonged. If this is the case, consider initiating combination therapy with one of the safer, first or second-line therapies and use the antipsychotic as a temporary bridge. If using antipsychotic medications, caregivers should be advised of the risks and asked for consent which should be documented in the patient's record. If the ISB stabilizes, attempt to deprescribe the antipsychotic within a few months. Finally, consider an antiandrogen such as MPA, CPA, or leuprolide in refractory cases. Given the numerous dangerous side effects of these medications, this should be done in consultation with geriatric psychiatry to ensure safer medications have been appropriately considered and tried first. Other review articles studying community dwelling patients reported cases of improvement with rivastigmine, quetiapine, leuprorelin, propranolol and pindolol[4,14,23]. Studies of these medications were not found in this review of ISB in long-term care homes, but may be of value in treatment of ISB.

Given the off-label use of all these medications in the treatment of ISB, we suggest a thorough discussion of the risks and benefits with the substitute decision maker and clear documentation of that process. Considering patient comorbidities and potential secondary indications of medications (agitation, depression, benign prostatic hyperplasia) can help guide therapy. As always, part of good prescribing is deprescribing. If a medication is not effective in controlling the symptom after a reasonable trial, then it should be weaned and discontinued.

Table 1. Evidence for pharmacological management of inappropriate sexual behaviours in patients with dementia residing in long-term care.

Medication Class	Medication & Dose	Study & Patient Details	Response
Antidepressants	Citalopram 10 – 40mg once daily[5,7]	Case report, 1 male, AD	Resolution
		Retrospective chart review 6 males, 1 female AD (3), VaD (2), mixed (2)	Partial (4) None (3) Worsening (1)
	Clomipramine 150 – 200mg once daily [13]	Case report, 2 males, AD	Resolution
	Mirtazapine 15 – 30mg once daily[5]	Retrospective chart review 1 male, VaD	Partial
	Paroxetine 20mg – 40mg once daily[11,12]	Case report, 1 male Alcohol related dementia	Resolution
		Case report, 1 male, FTD	Resolution
	Trazodone 100mg once daily[8]	Case report, 1 male, AD	Resolution
Antipsychotics	Aripiprazole 2.5 – 18mg once daily[15,16]	Case report, 1 female, AD	Resolution
		Case report, 1 male, FTD	Resolution
	Olanzapine 2.5 – 15mg once daily[5]	Retrospective chart review 5 males, 1 female AD (2), VaD (2), mixed (2)	Partial (6)
	Risperidone 0.5mg – 2mg[5,8]	Case report, 1 male, AD	Resolution
		Retrospective chart review 3 males, AD (1), VaD (2)	Partial (1) None (1) Worse (1)
	Risperidone 0.5 – 1.5mg or Haloperidol 0.5 –1.5mg per day[17] (dosing interval not reported)	Randomized double blind cross over study, n = 114 AD (79), VaD (34), mixed (7)	Risperidone was "significantly more effective in treating physical sexual advances"
	Quetiapine 12.5 –150mg[5]	Retrospective chart review 1 male, VaD	None
Anticonvulsants	Gabapentin 100mg BID, 200mg BID, or 300mg TID[20,21]	Case report, 3 males NPH (1), VaD (2)	Resolution
	Carbamazepine 800mg per day[22] (dosing interval not reported)	Case report, 1 male, FTD	Resolution
Mood stabilizer	Lithium 300 – 600mg[5] once daily	Case report, 1 male VaD with history of bipolar disorder	Partial resolution

AD = Alzheimer's disease, VaD = Vascular dementia, FTD = frontotemporal dementia, NPH = normal pressure hydrocephalus

MPA = medroxyprogesterone acetate, CPA = cyproterone acetate

Medication Class	Medication & Dose	Study & Patient Details	Response
Hormonal agents	MPA 5mg orally once daily[8]	Case report, 1 male, AD	Resolution
	MPA 100mg IM once monthly to 500mg IM once weekly[5,25–28]	Case report, 1 male, AD	Resolution
		Case report, 1 male, AD	Resolution
		Case report, 1 male, FTD	Resolution
		Case report, 5 males, AD (1), VaD (2), mixed (1), unspecified (1)	Resolution
		Case report, 5 males, AD (1), VaD (3), mixed (1)	Partial
	CPA 10mg orally once daily[31]	Case report, 2 males, VaD (1) Parkinson's dementia (1)	Resolution
	Conjugated estrogen 0.625mg – 2.5mg once daily[33,34]	Randomized double blind placebo-controlled study, n = 14, Dementia subtypes not reported	No significant improved in sexually aggressive behaviours
		Case report, 1 male, VaD	Partial
	Diethylstilbestrol 1mg once to twice daily [35]	Case report, 1 male, AD	Resolution
	Finasteride 5mg once daily[36]	Case report, 11 males, VaD (11)	Resolution (6) Partial (5)
Antihistamine	Cimetidine 400 –1600mg per day[3,37] (dosing interval not reported)	Case report, 1 male, VaD	Resolution
		Retrospective chart review 17 males, 3 female, dementia subtype not specified	Resolution (14) Partial (6)
Antifungals	Ketoconazole 100 – 200mg once daily[37]	Retrospective chart review 6 of 20 patients received ketoconazole and/or spironolactone in addition to cimetidine No other details reported	Resolution

AD = Alzheimer's disease, VaD = Vascular dementia, FTD = frontotemporal dementia, NPH = normal pressure hydrocephalus

MPA = medroxyprogesterone acetate, CPA = cyproterone acetate

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