Atypical Antipsychotic Agents - Guideline for use as part of the management strategy of behavioural and psychological symptoms of dementia (BPSD)

Site Applicability

All VCH-PHC Acute and Residential Sites

Practice Level

Physicians, Pharmacists, Nurse Practitioners

Practice Guideline

Purpose: The purpose of this guideline is to support clinicians in making informed decisions surrounding the use of atypical antipsychotic drugs as part of the management of aggression or agitation in patients with dementia in acute or residential care. Information on the reported risks and benefits of atypical antipsychotic use in this population has been consolidated and interpreted in the context of best practice recommendations.

Scope: Recommendations have been provided for the initial patient assessment on admission, the initial use of non-pharmacologic therapy at index episode of aggression or agitation, indication for drug therapy, involvement and documentation of informed consent of family/substitute decision-maker, initiation, careful titration and monitoring of drug therapy, documentation of effectiveness by 8 weeks, and documentation of review with a purpose to discontinue by 3 to 6 months when appropriate

Need to Know

Summary:

Goals: To support clinicians in drug-therapy decision making by providing current evidence with respect to reported risks and benefits. To encourage judicious and evidence-based use of drug therapy when instituted. To improve sharing of information with all care providers and family/substitute decision-makers.

Key Points:

Conduct patient assessment on admission to unit and before initiating drug therapy: Document baseline alertness, sedation, cognitive function, ADLs. Discourage telephone orders for initiating drug therapy & ensure work-up for contributing or reversible factors (such as: delirium, pain, discomfort, infection, loneliness, fear, boredom, drug side effects or interactions, environmental stress).

Non-drug interventions are considered first line before drug therapy by expert opinion: Given that not every patient will benefit from drug therapy & the possibility for harm, develop a patient/resident-centered psychosocial care plan & continue to optimize non-drug therapy even if drug therapy is initiated.

Recognize that the evidence base for drug therapy is modest: Debate exists surrounding magnitude of drug benefit due to inconsistent study results (including a high placebo response rate when drug effect is measured by clinicians) and limited applicability to all dementia subtypes encountered in clinical practice. At best, 1 in 5 patients will demonstrate benefit with drug therapy, at worst, 1 in 14 (that is, a number needed to treat that ranges from 5 to 14). Currently, however, atypical antipsychotics have a larger body of evidence in the management of BPSD than other drug therapies. Atypical antipsychotics are more likely to improve

aggressive rather than non-aggressive symptoms & are unlikely to benefit wandering, exit-seeking, disruptive vocalizations. There is no evidence for improvement in other important patient-centered outcomes such as: functional or cognitive abilities, quality of life, caregiver time needed.

Discuss the risks and monitor throughout drug therapy: Health Canada warnings between 2002 and 2005 report of an increased risk of mortality (largely due to cardiovascular events and infection) & cerebrovascular events based on results of drug studies. It has been estimated (when one considers the increased risk of mortality), that at best, 1 in 9 patients will benefit from drug therapy, at worst, 1 in 25 (that is, a number needed to treat that ranges from 9 to 25). Although many uncertainties remain, it is recommended that possible risks be discussed with all involved in care of patient prior to initiating drug therapy. Be vigilant for side effects that can emerge during drug therapy: extrapyramidal side effects (may affect 1 in 20 patients), tardive dyskinesia, anticholinergic toxicity, somnolence, abnormal gait, confusion & cognitive decline, falls, hypotension, ECG changes, peripheral edema, respiratory & urinary tract infections, metabolic changes.

Collaborate in team huddle prior to initiating drug therapy: Ensure optimization of psychosocial plan & identify as a team the urgency/time line for initiating drug therapy. Current guidelines suggest that drug therapy may be considered when *there is a significant risk of harm to patient or others or when agitation or aggressive symptoms are persistent, recurrent, or severe enough to cause significant suffering and distress, or significant interference with care*. Identify target symptom & provide documentation in chart. Share the decision making with family/substitute decision maker.

Unknown which atypical antipsychotic optimizes safety and efficacy: Currently only risperidone has Health Canada approval for short-term use for aggression ± psychosis. Risperidone, olanzapine have stronger evidence base than quetiapine but quetiapine is often chosen preferentially in Lewy Body Dementia & Parkinson's Disease Dementia due to an increased risk of extrapyramidal side effects in these patients.

Start with an appropriately low dose: Consider risperidone 0.25 mg per day, olanzapine 2.5 mg per day, quetiapine 12.5-25 mg per day as starting doses. Some side effects appear dose related & target doses remain poorly defined therefore aim for lowest effective maintenance dose.

Make a decision regarding effectiveness by 8 weeks: Monitor & document impact of drug therapy on symptoms using a behavioural chart. Follow frequency of symptoms, severity of symptoms, functional status, quality of life, & include healthcare provider/family/substitute decision-maker/patient (where possible) input.

Review for drug taper after a 3 to 6 month period of behavioural stability: The optimal duration of therapy is unknown due to relatively short duration of studies. Individualize treatment duration taking into account: patient's functional status, target symptom, duration/persistence/severity of symptoms.

Review of complete guideline is recommended for all physicians, nurse-practitioners and pharmacists involved at all levels of drug-therapy decision making for more complete information on key points

Patient assessment on admission to unit

- person-centered, sound admission process [1]
- document baseline alertness, sedation, cognitive function, ADLs [2]

Patient assessment on first episode

- assess, identify, and manage potentially reversible or contributing factors (eg delirium, pain, discomfort, infections, metabolic, neuropsychiatric, loneliness, fear, boredom, polypharmacy, drug interactions, environmental stress) [2-5]
- ensure appropriate tests ordered (e.g. chemistry, hematology, microbiology, radiology)
- ensure physical assessment; discourage telephone orders to initiate drug therapy

- gather information from family/substitute decision-maker and several staff members across different nursing shifts [1,2]
- behaviour analysis via ABC approach: Antecedants, Behaviours, Consequences [3,4]
- see also VCH Least Restraint and Maximizing Freedom: Residential Care guideline (currently in draft)

Initiate appropriate non-pharmacologic intervention

- first line intervention ahead of drug therapy in clinical practice guidelines [2,3]
- evidence suggests poor adherence to this recommendation [6,7]
- further study required to strengthen evidence base for specific interventions [2,5]
- in urgent situations, may initiate non-pharmacologic and drug therapy together [3]
- individualize a psychosocial care plan that emphasizes "interest, social activity, comfort" [2]
- continue to optimize non-pharmacologic interventions even if drug therapy is initiated [2]
- consult pharmacist to assess for possible medication-related contributors to onset of or change in behavioural or psychological symptoms as soon as possible
- see also VCH Least Restraint and Maximizing Freedom: Residential Care guideline (currently in draft)

Current evidence base for efficacy

- available data: inconsistent results, small RCTs with methodologic limitations, short duration generally up to 12 weeks, prominent placebo response rates (30-40%), highly selected patients [2,8-10]
- majority of data involves patients with Alzheimer's and Vascular Dementia; evidence may be less applicable to other subtypes [11,12]
- debate regarding clinical significance of trial outcomes [8,11,13,14]
- currently, larger evidence base exists for antipsychotics than for other pharmacologic interventions [9,11,13]; paucity of comparative trials
- evidence base is more robust for aggressive than non-aggressive symptoms (e.g. agitation, hallucinations, delusions); many trials measured global behavioural disturbance therefore it is difficult to separate out the effects on specific symptoms [2,15-18]
- some behaviours unlikely to respond: wandering, exit-seeking, disruptive vocalizations [3]
  - o "*should not be viewed as broad spectrum agents*" [19]
- NNT= 6 commonly referenced in professional presentations but may range from 5-14 [8] (derived from a small number of diverse RCTs demonstrating nominal statistical significance on symptom scales; it is possible that careful patient selection by experienced clinicians caring for patients with severe target symptoms unresponsive to non-pharmacologic intervention may reduce this NNT
- CATIE-AD (non-industry sponsored, outpatient RCT) showed for every 10 patients treated ~ 2 will remain on therapy @ 36 weeks [20]
- given the modest benefit afforded by these agents, concordance with prescribing guidelines does not guarantee improvement in symptoms [21]
- no RCT evidence of benefit on functional abilities, QOL, caregiving time needed [18]
- do not improve cognitive deficits of dementia; may further cognitive impairment, confusion [8,18,20,22]

Risks

- incomplete reporting of harms in RCTs [23,24]
- risk associated with longer-term use (> 10-12 weeks) unknown
- treatment-emergent ADRs [8]:
  EPS (NNH = 20), TD, anticholinergic toxicity, somnolence (NNH = 10), abnormal gait (NNH=13), confusion, falls, hypotension, ECG abnormalities, peripheral edema (NNH = 20), UTIs (NNH = 25), RTIs, metabolic including worsening hyperglycemia, weight gain, cognitive decline (i.e. ↓ 0.7 of an MMSE point over 6-12 weeks)
- in CATIE-AD, discontinuation due to intolerance, ADRs, death favoured placebo over all 3 drugs (risperidone, olanzapine, quetiapine) [20]

- increased risk of mortality (largely due to CV events eg heart failure, sudden death and infection e.g. pneumonia)
  - Health Canada warning June 2005 [25]
  - NNH = 100 by independent meta-analysis [26] (15 short-term RCTs over 10-12 weeks)
    3.5% vs 2.3%
    pooled results for risperidone, olanzapine, quetiapine, aripiprazole
  - unclear if pre-existing risk factors affect risk
  - insufficient information on cause of death
  - nonrandomized data suggest risk may be similar [27,28] or possibly higher [29-32] with typical (compared to atypical) antipsychotics
- increased risk of cerebrovascular events (CVAEs)
  - Health Canada warning October 2002 [33] (risperidone), March 2004 [34] (olanzapine)
  - NNH = 71 by independent meta-analysis [35] (11 short-term RCTs)
    2.2% vs 0.8%
    pooled results for risperidone, olanzapine only
  - overall rate of CVAEs may not indicate increased risk of serious events (eg stroke)
  - unclear if pre-existing risk factors affect risk
  - causative pathophysiology unknown; association requires further clarification [35]
  - several methodologic issues identified, conflicting observational data [35]
- short-term RCTs suggest atypicals are less likely to cause EPS or exacerbate TD than typicals (however comparisons only exist for haloperidol); no additional therapeutic advantages have been established [16]
  - short-term RCTs cannot provide adequate data on risk of movement disorders with long-term use [23,36]
  - observational data over the longer term suggests this advantage may be lost at higher doses [36,37]
  - in CATIE-AD, the incidence of parkinsonism or EPS was 12% for both the olanzapine group (mean dose 5.5 mg per day) and the risperidone group (mean dose 1 mg per day) versus 2% for the quetiapine group (mean dose 56.5 mg per day) [20]; the quetiapine dose utilized was lower than that of earlier trials [8]
- direct RCT comparisons between typical and atypical agents are limited, therefore the differential effects of these agents on adverse events such as CVAEs and mortality is uncertain [16]
  - an analysis of the impact of regulatory warnings on prescription rates demonstrated after the first Health Canada warning in October 2002 (for risperidone) a subsequent increase in quetiapine use and typical antipsychotic use [38], however given the minimal within-class and between-class comparisons this is not an evidence-based strategy for minimizing specific risks
  - rather, individualized decision making taking into account each patient's risk factors for particular adverse events is recommended [16]
  - recognize that *"the same drugs may not be equally effective and/or safe in all elderly patients"* [2]

Drug decision making

- team huddle prior to initiating drug therapy to coordinate care with other health-care professionals [16,23,39]
- considerable debate regarding the threshold for prescribing atypical antipsychotics in BPSD [40-42], current guidelines suggest that antipsychotics be used when:
  there is a significant risk of harm to the patient or others or when agitation or aggressive symptoms are persistent, recurrent, or severe enough to cause significant suffering and distress, or significant interference with care [2,3,43,44]
- a 2004 expert consensus document did not recommend their use in panic disorder, generalized anxiety disorder, nonpsychotic major depression, hypochondriasis, irritability, hostility, sleep disturbance, neuropathic pain, severe nausea, motion sickness in the absence of a major psychiatric syndrome [45]
- *"likelihood of helping vs harming"* has been estimated at NNT = 9-25 when one balances the evidence of efficacy with the evidence for increased mortality [26] (see earlier limitation of NNT); however this estimate will not help a clinician identify which patient is likely to respond and which patient is at risk for harm

- consider role of non-antipsychotic agents where appropriate (see references 3,4,16); optimize treatment of comorbid neuropsychiatric symptoms (eg depression, anxiety) with evidence-based therapies
- identify target symptom, ensure documentation
- identify whether target symptoms are likely to respond to drug therapy; and consider that not all symptoms require pharmacotherapy [16]
- identify dementia subtype where possible and consider:
  - majority of RCTs included patients with Alzheimer's and Vascular Dementia [11,12]
  - Lewy Body and Parkinson's Disease Dementia subtypes are considered to be more vulnerable to extrapyramidal side effects [3,45,46]
- determine urgency/time line for initiating drug therapy
  - some symptoms resolve without drug therapy over a period of days to weeks [15]
  - may consider a period of observation unless symptoms are extremely distressing [16,47]
- involve family/substitute decision-maker in decision making regarding treatment options; adequately inform of risks/benefits, obtain and document consent [2,16]
- assess risk factors for stroke, MI, ECG abnormalities, aspiration pneumonia, other infection [2]

Which atypical

- insufficient data to guide which drug optimizes safety and efficacy [23,48]
- currently risperidone is the only agent approved by Health Canada for: *"short-term symptomatic management of inappropriate behaviour due to aggression and/or psychosis"* in dementia [49]
- specifically, a Cochrane review finds evidence for risperidone and olanzapine in the management of *aggression*; and risperidone for *psychosis* [11]
- risperidone, olanzapine have stronger evidence base than quetiapine [4,10-13]
- in CATIE-AD, median time to discontinuation due to lack of efficacy favoured olanzapine (22.1 weeks) and risperidone (26.7 weeks) over quetiapine (9.1 weeks) and placebo (9 weeks) [20]; the quetiapine dose utilized was lower than that of earlier trials [8]
- multiple analyses find insufficient RCT evidence to evaluate quetiapine [8,10-14]
  - however, quetiapine generally recommended in Lewy Body Dementia and Parkinson's Disease Dementia over other antipsychotics [3,45]; hypothesized to decrease the risk of neuroleptic malignant syndrome and movement ADRs in the "EPS-vulnerable" patient [46]

Which dose

- some ADRs appear to be dose related (hypotension, gait disturbances, EPS, somnolence, anticholinergic side effects) [2,16,23,36,50,51]
- start with an appropriately low dose [52,53]
  - risperidone 0.25 mg per day
  - olanzapine 2.5 mg per day
  - quetiapine 12.5-25 mg per day
- aim for the lowest effective maintenance dose [3,4,16]
- may consider target doses but recognize these ranges are not universally accepted given the limited number of trials assessing optimal dosing [16]; except for CATIE-AD [20] most RCTs used fixed dosing
  - risperidone 0.5-1.5 mg per day
  - olanzapine 5-10 mg per day
  - quetiapine 50-200 mg per day
- generally given as a one time daily dose (at bedtime for olanzapine, quetiapine) or divided into a twice daily dose [54]; half life is sufficient such that dividing the dose more than twice a day or targeting specific hours of the day with maintenance dosing is probably unnecessary
- optimal dose for quetiapine inadequately studied and complicated by one RCT suggesting a minimum effective dose of 200 mg per day on measures of agitation [55]
- recognize it is not known if dosing modifies the risk of CVAEs, mortality [51]

- the safety and efficacy of single doses (PRN dosing) has not been evaluated or compared in clinical trials to other PRN agents (such as typical antipsychotics or benzodiazepines), and the onset of action of atypical antipsychotics has not been clearly defined [41,56]
  - in practice this strategy has been used by our expert panel in select situations: to determine the need for a maintenance dose [52,57], during the dose titration phase in conjunction with regular dosing [57], in advance of unavoidable activities know to trigger significantly aggressive or agitated behaviour [52], and for anticipated but intermittent behaviours [52]
  - if employed, ensure effective documentation systems in place: specify indication for PRN doses (e.g. specific behaviour) and include documentation via ABC approach (Antecedants, Behaviours, Consequences);
  - regular assessment of ongoing PRN orders are recommended in order to ensure appropriateness and to determine if a modification to maintenance dose is needed [52,57]
  - quetiapine is commonly utilized over other atypicals as a PRN agent when insomnia is present as part of the BPSD picture [53] however its use as a sedative for primary insomnia outside the setting of agitated and aggressive behaviours is generally not recommended [45]

Monitoring

- consider the following parameters when assessing effectiveness [16]:
  - frequency of symptoms
  - severity of symptoms
  - functional status
  - quality of life
  - healthcare provider, caregiver, family/substitute decision-maker, and patient (where possible) input
- document impact on symptoms using an observational chart [4]; for example, see the VCH CPD: Identification of Agitated & Excessive Behaviours & Client-Centered Interventions
- consider follow-up intervals: 1 week after initiation; 10 days after dose change [45]
- some symptoms improve in the first 2 to 4 weeks of drug therapy [16]; our content expert panel suggests making a decision regarding effectiveness by 8 weeks
  - some symptoms may respond earlier than others to drug therapy [52]
  - no rationale for extending therapy outside length of RCTs (10 to 12 weeks) if no benefit [8]
  - document when and what benefit is observed in the chart
- the median time to discontinuation due to treatment failure in CATIE-AD (outpatient RCT) ranged from 5 to 8 weeks [20]
- be vigilant for treatment-emergent and dose-related ADRs (see Risks and Which Dose)
- periodic physical assessments should include an assessment for movement-related ADRs (eg EPS, TD)
- monitoring for metabolic ADRs such as hyperglycemia (observational evidence exits for worsening hyperglycemia in the elderly with diabetes [58]), dyslipidemia (olanzapine associated with ↓ HDL in CATIE-AD [59]), weight gain (olanzapine, quetiapine in particular associated with weight gain in women in CATIE-AD [59]) has been recommended [16] however the *clinical relevance* of these surrogate markers in this patient population has not been determined
  - consider that changes in weight may occur independently of metabolic alterations and may reflect, rather, a change in the individual's functional status while on drug therapy; for example, a patient with poor baseline nutritional status may gain weight if BPSD symptoms and, subsequently, oral intake improves; conversely, a patient with weight loss should be assessed for worsening BPSD symptoms or excess somnolence which may be negatively affecting oral intake
- reduce dose or discontinue if evidence of substantial QT prolongation on ECG [42:]; the benefit of baseline or routine monitoring has not been determined

Duration of therapy

- risk and benefit of long-term use outside the scope of short-term RCTs (up to 12 weeks) is not known [15]
- longer term trials (up to 12 months) have not shown consistent benefit [20,22,60]

- for some patients, symptoms wax and wane, and may attenuate over time particularly in the case of Alzheimer's Dementia where hallucinations tend to resolve over a period of a few months, but delusions, aggression, and agitation may be more persistent [61]
- documentation of ongoing evaluation and the need for medication continuation should be regularly reassessed [51]
- provincial [43,54], national [3,62], and international [16,39,44,63,64] guidelines recommend periodic attempts to taper and discontinue after a period of symptomatic remission
- in practice, efforts to stop or dose reduce appear to be infrequent [6,65]
- a few RCTs indicate successful drug withdrawal after a period of behavioural stability [60,66-70]
- recognize it is not known if duration of therapy modifies the risk of CVAEs, mortality
- there is considerable uncertainty regarding optimal treatment duration
  - current Canadian guidelines recommend 3-6 months [3,62]; this also reflects the range of opinion of our content expert panel: some recommend 3 months of behavioural stability to be an appropriate goal for taper assessment, others 6 months
  - appropriate length of therapy should be individualized and may depend on the patient's functional status, the target symptom, and the duration, persistence, and severity of symptoms
- anecdotal clinical experience suggests some patients require maintenance therapy [68]
- even if benefit is documented, review patient at periodic intervals
- taper attempt may be considered

Expected Client/Family/Substitute Decision-Maker Outcomes

Judicious use of atypical agents with the aim to optimize treatment of significant behavioural and psychologic symptoms

Reduced risk of unnecessary drug exposure, therefore avoidance of adverse events

Improved sharing of information of risks and benefits of treatment with family/substitute decision-maker and care providers

Documentation

- **Patient admission:** document baseline alertness, sedation, cognitive function, ADLs
- **Non-pharmacologic:** document psychosocial care plan
- **Drug decision making:** identify and document dementia subtype where possible; identify and document target symptoms; specify indication for PRN doses
- **Informed consent:** document that possible risks and benefits have been explained to all care providers and family/substitute decision-maker
- **Monitoring:** document impact on symptoms using an observational chart ; document what and when benefit is observed; document decision regarding effectiveness by 8 weeks
- **Duration:** document assessment for taper every 3 to 6 months

Related Documents

- VCH CPD: Identification of Agitated & Excessive Behaviours & Client-Centered Interventions
- VCH Least Restraint and Maximizing Freedom: Residential Care (Currently in Draft)

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