# Quick Facts on Atypical Antipsychotics at End-of-Life

The antipsychotic class of medications is comprised of two classes:

- First generation, or conventional (i.e., haloperidol, chlorpromazine)
- Second generation, or atypical (i.e., risperidone, olanzapine, quetiapine)

The atypical class has a lower risk of side effects compared to conventional agents[1,2], all antipsychotics have potential to cause the following:

- Extrapyramidal symptoms (EPS): Akathisia, dystonia, pseudoparkinsonism, dyskinesia
- QT interval prolongation: If possible, avoid use in patients with long QT syndrome, history of cardiac arrhythmias, or prescribed concomitant medications that prolong the QT interval
- Metabolic adverse effects: Weight gain, hyperglycemia, hyperlipidemia

Atypical agents are approved for the indications: schizophrenia, bipolar disorder, adjunct to antidepressants for depression, schizoaffective disorder, agitation due to autistic disorder and Tourette's syndrome.[3] They are also used off-label for various indications including agitation and delirium, which are the most common symptoms for which they are prescribed in hospice.[4,5]

## AGITATION AND USE OF ATYPTICALS IN DEMENTIA

Atypicals are often used to treat the behavioral and psychological symptoms of dementia (BPSD) despite lack of approval for this indication by the FDA and concerns about efficacy and safety. Recent studies found that atypical antipsychotics are ineffective in managing disruptive behavior in older dementia patients. Moreover, safety issues including the potential risk for developing acute extrapyramidal side effects (e.g. akathisia, pseudoparkinsonism, and dystonia), postural hypotension, somnolence, falls, and prolonged QT syndrome may outweigh any perceived benefits.[6-9]

In addition, an analysis of 17 placebo-controlled trials showed that mortality was increased when antipsychotics (both conventional and atypicals) were used to treat BPSD in older patients with dementia. The risk of death in patients using atypicals was 1.6 to 1.7 times the risk in the placebo group, with death most commonly occurring from heart failure, sudden death and pneumonia. This study resulted in the addition of a black box warning to the labeling of both atypical and conventional antipsychotics in April 2005.[10-12]

## WHEN IS ANTIPSYCHOTIC USE APPROPRIATE FOR AGITATION?

Antipsychotics are only indicated when symptoms persist despite non-pharmacological and medication interventions:

- For a labeled indication (See **Appendix 1** for a medication-specific list)
- Behavioral symptoms due to mania or psychosis
- Symptoms present a danger to the patient or others
- Patient is experiencing inconsolable or persistent distress
- Patient is experiencing a significant decline in function or substantial difficulty receiving needed care

Antipsychotics should **NOT** be used for purpose of:

- Sedation, restraining, wandering, poor self-care, impaired memory, inattention or indifference, uncooperativeness, fidgeting, mild anxiety, insomnia, restlessness, nervousness, sadness or crying (not related to depression or psychiatric condition)

## DELIRIUM

Delirium occurs commonly in palliative care and manifests as cognitive changes, perceptual disturbances, and behavioral agitation. When the underlying cause cannot be identified and/or cannot be reversed, the standard first-line therapy for delirium typically includes conventional antipsychotics. They reduce psychosis and agitation and provide some degree of sedation without providing amnesia, muscle relaxation or an anti-seizure effect. Note that little evidence exists stating that atypical antipsychotics are more efficacious than conventional agents for managing delirium.[5]

Although generally accepted as effective and appropriate by the medical community, antipsychotics for delirium have not been evaluated in large placebo-controlled trials and results are inconsistent, making them difficult to apply to palliative care.[5] However, a recent double-blind, parallel-arm, randomized control trial of 247 palliative patients with delirium compared the efficacy of risperidone or haloperidol to placebo and found that antipsychotic drugs were not useful in reducing distressing symptoms.[13,14] This study was not without limitations and the results should be evaluated critically against practitioner experience.

## ATYPICAL ANTIPSYCHOTIC DISCONTINUATION STRATEGY IN HOSPICE[15-20]

Considering the limited benefits and increased risks, the ongoing use of atypical antipsychotic drugs in hospice patients should be regularly reevaluated. When it is determined that atypical antipsychotics no longer meet the patient's goals of care, a strategy for drug discontinuation should be considered. This plan involves an open discussion with patients, families, and caregivers about the possible effects of discontinuing atypical antipsychotics. Patients should be monitored and educated about potential **withdrawal side effects** and **rebound syndromes** including:

- Withdrawal symptoms- agitation, restlessness, confusion, poor appetite, weight loss, sleep disturbances, motor problems
- Cholinergic rebound- insomnia, nausea, vomiting, profuse sweating, malaise
- Rebound psychosis- new or worsening agitation, aggression, or behavioral symptoms

Current guidelines have not established any hard-and-fast rules that specifically outline the steps for discontinuing atypical antipsychotics. However, there are two general approaches which can be applied, involving either an **abrupt discontinuation** or a **gradual dose reduction**. Tips to consider when making a decision about which discontinuation strategy to use include the following key points:

- **Abrupt Discontinuation**- In the event of serious side effects (e.g. agranulocytosis, tardive dyskinesias, neuroleptic malignant syndrome), it may be necessary to immediately discontinue treatment with atypical antipsychotics.
- **Gradual Dose Reduction**- Tapering or weaning minimizes the risk of withdrawal symptoms and rebound syndromes by allowing the body time to readjust to changing levels of neurotransmitters in the brain. A common practice adopts a method of ***go slow as you start to go low***. Suggested practice includes weaning by reducing the dose 25% each week.

Whether an atypical antipsychotic treatment is abruptly stopped or gradually tapered, the patient will require close monitoring to address possible undesired effects.

**Appendix 1:** Atypical Antipsychotic Indications and Average Cost[2,3]

| Drug/dosage form | Average Cost (15-day supply) | Labeled Indications | | | | | | | | | Off-label Indications | | | | | | *Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Schizophrenia | Bipolar disorder | Bipolar depression | Bipolar mania | Major depressive disorder (adjunct to antidepressants) | Agitation associate with psychosis or bipolar mania | Schizoaffective disorder | Autistic disorder | Tourettes syndrome | Agitation associated with dementia | Dementia w/ Lewy bodies | Borderline personality disorder | Depression monotherapy | Delirium in pediatric ICU | Oppositional defiant disorder | |
| Clozapine (Clozaril®)[α] PO tab | $50-100 | X | X* | | | | | X | | | X | | | | | | Off-label |
| Clozapine[α] ODT (12.5mg, 25mg, 100mg) | $50-100 | X | X* | | | | | X | | | X | | | | | | Off-label |
| Quetiapine (Seroquel®) PO tab (25mg, 50mg, 100mg) | $150-200 | X | X | X | X | X | | | | | X | X | X | X | | | |
| Risperidone (Risperdal®) PO tab & oral soln | $150-200 | X | X | | X | | | | X | X* | X | | | | X | X | Off-label |
| Ziprasidone (Geodon®) PO cap | $100-150 | X | X | | X | | | | | X* | X | | | | | | |
| Olanzapine (Zyprexa®) PO tab | $300-350 | X | X | X* | X | X* | | | | | X | | | | | | Combo w/ Fluoxetine |
| Olanzapine (Zyprexa Zydis®) ODT | $350-400 | X | X | X* | X | X* | | | | | X | | | | | | Combo w/ Fluoxetine |
| Quetiapine (Seroquel® XR) PO tab, ER | $300-350 | X | X | X | X | X | | | | | X | X | X | X | | | |
| Risperidone (Risperdal M-tab®) ODT | $250-300 | X | X | | X | | | | X | X* | X | | | | X | X | Off-label |
| Aripiprazole (Abilify®) PO tab | $450-500 | X | X | | X | X | X | | X | X | X | | | | | | |
| Aripiprazole (Abilify Discmelt®) ODT | $550-600 | X | X | | X | X | X | | X | X | X | | | | | | |
| Asenapine (Saphris®) SL tab | $600-700 | X | X | | X | | | | | | X | | | | | | |
| Clozapine[α] ODT (150mg, 200mg) | $400-450 | X | X* | | | | | X | | | X | | | | | | Off-label |
| Lurasidone (Latuda®) PO tab | $650-700 | X | | X | | | | | | | X | | | | | | |
| Paliperidone (Invega®) PO tab, ER | $650-700 | X | X* | | X* | | | X | | | X | | | | | | Off-label |
| Quetiapine (Seroquel®) PO tab (200mg, 300mg, 400mg) | $400-500 | X | X | X | X | X | | | | | X | X | X | X | | | |
| Clozapine (Clozaril®)[α] oral susp | $900-950 | X | X* | | | | | X | | | X | | | | | | Off-label |
| Iloperidone (Fanapt®) PO tab | $800-850 | X | | | | | | | | | X | | | | | | |
| Aripiprazole (Abilify®) oral soln | >$1,000 | X | X | | X | X | X | | X | X | X | | | | | | |

[α]In September 2015, the FDA announced approval of a shared risk evaluation and mitigation strategy (REMS) called the Clozapine REMS Program. All patients receiving clozapine must be enrolled in the Clozapine REMS Program, and all prescribers and dispensing pharmacies of clozapine are required to be certified in the Clozapine REMS Program.

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| | | Schizophrenia | Bipolar disorder | Bipolar depression | Bipolar mania | Major depressive disorder (adjunct to antidepressants) | Agitation associate with psychosis or bipolar mania | Schizoaffective disorder | Autistic disorder | Tourettes syndrome | Agitation associated with dementia | Dementia w/ Lewy bodies | Borderline personality disorder | Depression monotherapy | Delirium in pediatric ICU | Oppositional defiant disorder | |
| Olanzapine (Zyprexa IntraMuscular®) IM (10mg) | $50-100 | X | | | | | X | | | | | | | | | | |
| Paliperidone (Invega Sustenna®) IM (39mg) | $100-150 | X | | | | | | X | | | | | | | | | |
| Risperidone (Risperdal Consta®) IM (12.5mg) | $200-250 | X | X | | | | | | | | | | | | | | |
| Paliperidone (Invega Sustenna®) IM (78mg) | $450-500 | X | | | | | | X | | | | | | | | | |
| Ziprasidone (Geodon®) IM (20mg) | $450-500 | X | | | | | | | | | | | | | | | |
| Risperidone (Risperdal Consta®) IM (25mg) | $500-550 | X | X | | | | | | | | | | | | | | |
| Risperidone (Risperdal Consta®) IM (37.5mg) | $700-750 | X | X | | | | | | | | | | | | | | |
| Paliperidone (Invega Sustenna®) IM (117mg, 156mg) | >$1,000 | X | | | | | | X | | | | | | | | | |
| Risperidone (Risperdal Consta®) IM (50mg) | >$1,000 | X | X | | | | | | | | | | | | | | |
| Aripiprazole (Abilify Maintena®) IM (400mg) | >$2,000 | X | X | | X | | X | | | | | | | | | | |
| Paliperidone (Invega Sustenna®) IM (234mg) | >$4,000 | X | | | | | | X | | | | | | | | | |

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