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Approaches to Gradual Dose Reduction of Chronic Off-Label Antipsychotics Used for Behavioral and Psychological Symptoms of Dementia

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Abstract

OBJECTIVE: Little is known about how to best taper antipsychotics used in patients with dementia. To address this gap, we reviewed published antipsychotic discontinuation trials to summarize what is known about tapering strategies for antipsychotics used with older adults with dementia. We further developed pharmacokinetic-based gradual dose reduction (GDR) protocols based on antipsychotic half-lives.

DATA SOURCES: MEDLINE, EMBASE, and International Pharmaceutical Abstracts were searched up to October 2014 to identify intervention studies reporting the behavioral and psychological symptoms of dementia outcomes resulting from discontinued off-label use of antipsychotics in nursing facility populations. Recently published pharmacokinetic reviews and standard pharmacology texts were used to determine antipsychotic drug half-lives for the pharmacokinetic-based GDR protocols.

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STUDY SELECTION: For the review, studies with an intervention resulting in antipsychotic medication discontinuation or tapering were eligible, including randomized controlled trials and pre- and post-intervention studies.

DATA EXTRACTION: When available, we extracted the protocols used for antipsychotic GDR from each study included in the review.

DATA SYNTHESIS: We found that clinical trials used different approaches to antipsychotic discontinuation, including abrupt discontinuation, slow tapers (more than two weeks), and mixed strategies based on drug dosage. None of the published trials described an approach based on pharmacokinetic principles. We developed a two-stage GDR protocol for tapering antipsychotic medications based on the log dose-response relationship; each stage was designed to result in a 50% dose reduction prior to discontinuation. This pharmacologically based strategy for patients chronically prescribed antipsychotics resulted in recommendations for slow tapers.

CONCLUSION: Our theoretically derived GDR recommendations suggest a different approach than previously published in clinical trials. Further study is needed to evaluate the effect of this approach on patients.

Keywords

Antipsychotics; Dementia; Dose reduction; Gradual dose reduction; Off-label; Tapering

Introduction

The off-label use of antipsychotic medications for the treatment of the behavioral and psychological symptoms of dementia (BPSD) is both pervasive and controversial.[1,2] Up to 80% of patients with dementia experience BPSD, which includes agitation, verbal outbursts, and physical aggression that can be personally distressing to the patient and disruptive to nursing facilities.[3] Prevalence rates of antipsychotic use for nursing facility residents with dementia remain high despite Food and Drug Administration (FDA) “black box” warnings in 2005 and 2008 and a growing body of research suggesting that their use comes with increased risk of mortality and only mild-to-moderate benefits.[4–10]

A goal in treating frail older adults is to reduce the use of unnecessary medications.[8] Additionally, in the United States, regulations enacted under the Omnibus Budget Reconciliation Act of 1987 (OBRA) consider the off-label use of antipsychotics to manage BPSD as an undue use of chemical restraints.[11] For these reasons, regulatory guidance for nursing facilities in the United States requires facilities to ensure that “[r]esidents who use antipsychotic drugs receive gradual dose reductions, and behavioral interventions, unless clinically contraindicated, in an effort to discontinue these drugs.”[12]

Unfortunately, once prescribed, most nursing facility residents with dementia remain on these drugs indefinitely, without attempts to taper them.[13] To our knowledge, neither the medical literature nor OBRA regulations offer specific guidelines on how to taper antipsychotic medications used for BPSD in elderly patients. This paper is aimed at helping clinicians avoid abrupt antipsychotic discontinuation in elderly persons with dementia. Adverse drug withdrawal events are especially prevalent in the nursing facility setting and

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broadly include a recurrence of the underlying symptoms that the medication was originally used to treat, true physiological or psychological withdrawal reactions, or new symptoms.[14,15]

With regard to adverse drug withdrawal events with antipsychotic agents, the primary concern is recurrence of behavioral symptoms. Physiological withdrawal reactions from antipsychotics are also concerning (e.g., dyskinesias, insomnia, nausea, restlessness), as they can be similar to the underlying condition for which the antipsychotic was prescribed. After an abrupt or rapid taper of an antipsychotic, if an individual is restless or agitated, it may not be an exacerbation of BPSD in the absence of treatment, but rather antipsychotic withdrawal symptoms.[15–17] This is similar to what occurs with rapid or abrupt tapering of benzodiazepines.[18] We know from reports about drug withdrawal for antipsychotics used among patients with schizophrenia that abrupt discontinuation of antipsychotic maintenance treatment is associated with greater risk of early relapse than gradual (over three or more weeks) tapering.[19] Kinetics are profoundly affected by frailty and sarcopenia, which may alter the distribution and compartmentalization of individual agents. The increased risk of early relapse exceeds what would be expected as a result of untreated psychosis; since the time frame for early relapse is consistent with the elimination of antipsychotics from the body, recurrent symptoms may reflect withdrawal as a result of pharmacodynamic adaptations from chronic treatment.[19] Pharmacodynamics are widely unpredictable given the interindividual variability in various receptor activity. There is concern about the risk for adverse drug withdrawal events despite conflicting evidence from clinical trials that suggests that antipsychotic drugs used long-term can be withdrawn from patients with dementia without detrimental effects on their behavior.[20]

Evidence from conflicting clinical trials, retrospective studies, and case studies suggest that in some cases, BPSD increase after discontinuation occurs, providing some evidence for withdrawal symptoms in older adults.[21–24] Since gradual tapering may also alleviate antipsychotic withdrawal symptoms, a pharmacokinetically driven tapering strategy for off-label use of antipsychotics among older adults with BPSD may lead to more favorable outcomes than abrupt discontinuation or rapid tapering.[16,25]

While the need to taper with gradual dose reductions (GDRs) may be well understood, characterization of tapering of individual antipsychotics used in patients with dementia, and more information on how to implement a very gradual taper, may be useful. This narrative review was conducted to summarize the protocols used for tapering or discontinuing antipsychotic medications for these patients. This narrative review aims to: 1) summarize what is currently known about protocols for GDRs of antipsychotic medications among individuals with dementia, and 2) use pharmacokinetic principles to develop a theoretically based protocol for antipsychotic GDR. This is a comparison of the published protocols to the pharmacologically based protocol to shed light on the controversy regarding antipsychotic GDR in frail older adults with dementia. The end result of this review will be an empirically informed, theoretically derived guideline for tapering strategies for various commonly used antipsychotic medications and suggestions for implementing such tapering schedules for elderly patients with dementia.

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Methods

This study was not human subjects research and as such did not undergo ethics review.

Literature Review

To summarize what is currently known about protocols for GDRs of antipsychotic medications among individuals with dementia, a review was conducted of intervention studies reporting the BPSD outcomes resulting from discontinued off-label use of antipsychotics in nursing facility populations.

Medline, EMBASE, and International Pharmaceutical Abstracts were initially searched up to October 2011, and updated on October 10, 2014. Studies were not excluded based on date of publication. The MEDLINE search strategy included searches on the following: ("antipsychotic drugs" or "neuroleptics"), ("tapering" or "withdrawal), "dementia," "nursing facility." This approach was also employed for the other databases, keeping subject headings and key words as similar as possible. There is no registered review protocol for this study.

Studies with an intervention resulting in antipsychotic medication discontinuation or tapering were eligible, including randomized controlled trials, and pre- and postintervention studies. At least three investigators (JLD, AK, JT) reviewed all articles for final inclusion. If investigators disagreed, the team discussed the articles until consensus was reached. Of the eligible articles, reference lists were reviewed to identify additional original studies relevant for the narrative review. We extracted the protocol used for antipsychotic GDR in each study. If the protocol for antipsychotic GDR was not provided, we indicated this in our review. Data were extracted to an electronic spreadsheet by one author (JNH) and independently reviewed by two other authors (KLL and JT).

Developing Pharmacokinetic-Based GDR Recommendations

Theoretical Framework: Pharmacokinetic Principles in Older Adults—In older adults, age-related physiologic changes that alter the pharmacokinetics of a drug must be taken into consideration with prescribing and changing doses of medications.[26] These include slowing of the biotransformation of drugs by the liver and excretion by the kidneys. In addition, when diseases of either of these organs occurs, the slowing of drug elimination may be less rapid than the recommendations, summarized in the tables that follow. It is always advisable to calculate the renal function of older adults because those with low-muscle mass may have a creatinine-formation rate too slow to raise the serum creatinine above usual normal values, despite substantial decrease in renal function. Other confounding conditions such as congestive heart failure or chronic liver disease can also slow drug elimination. The knowledge of the pharmacokinetics of the drug to guide dosage in individualizing therapy for patients will be improved the more a drug is studied in elderly patients and in patients with these confounding conditions.[27–29] The suggestions in our tables are for average elderly without major confounding illness that would affect drug elimination.

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Method for Developing GDR Intervals

We developed a protocol for tapering medications that has two stages of 50% dosage reductions, based on the log dose-response relationship, prior to discontinuation. The intervals between reductions are related to drug half-life. This theoretically derived tapering schedule is predicted to result in slower gradual drug-level reductions and ultimately better clinical outcomes (i.e., fewer behavioral recurrences) than with a more rapid taper. We calculated intervals between each dose change based on the pharmacokinetics of drug clearance in older adults. Since the half-lives of drugs in older adults are longer than in the usual subjects of pharmacokinetic research studies, we adjusted the predicted half-life accordingly based on age. Ideally, age, frailty, disease burden, drug burden, and hepatic enzyme activity should be considered. Our goal, however, was to develop an approach with minimal data available. For those 65 to 89 years of age, we adjusted half-lives by 1.5 times, and for those 90 years of age and older, we adjusted the half-life by two times. Drug half-lives were determined from recently published pharmacokinetic reviews and standard pharmacology texts.[26,30–32] Since the reported half-lives were similar between the pharmacology text and the systematic reviews, we ultimately used the values in the pharmacology texts for our interval calculations. We then calculated intervals between dose adjustments to reflect time needed to reach serum steady-state, which is five to seven drug half-lives. When drugs had an active drug metabolite, the half-life of the active metabolite was used for the calculation when appropriate; otherwise, the half-life of the parent drug was used. When the resulting times between dose adjustments resulted in a specific number of days (e.g., 41 days for aripiprazole [Table 1]), we rounded up the value to increments of weeks for practicality.

Results

Published Tapering Protocols

The literature review resulted in the inclusion of 14 studies that reported BPSD outcomes following an intervention to reduce antipsychotics.[24,33–45] Of the 11 studies that were experiments, 9 randomized individual patients, 1 was a cluster randomized trial design, and 1 was a nonrandomized controlled trial.[24,33–42] The three nonexperimental studies were pre/post studies.[43–45] Eight studies were conducted solely in nursing facility residents with dementia.[34,37,38,41–45] Four studies recruited from both nursing facility residents and external populations.[24,35,36,40] This included two studies that recruited from both assisted living facility and nursing facility residents with dementia, one study that recruited both nursing facility residents with dementia and hospital patients with dementia on a geriatric chronic care floor, and one study that recruited nursing facility or assisted living facility residents with dementia and outpatients with dementia.[24,35,36,40] Two studies recruited only participants not living in nursing facilities.[33,39] This included one study that recruited solely from a psychogeriatric ward and one study that recruited only outpatients with dementia.[33,39]

Table 2 summarizes the trials that focused on directly discontinuing antipsychotic medications. The antipsychotics targeted for tapering and the specific tapering protocol are shown by type of taper (i.e., abrupt, short-term tapering, mixed strategy). Three studies used

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an abrupt approach.[24,36,37] Risperidone and haloperidol were included in all three studies. Four studies were conducted that used a short-term tapering protocol.[33–35,45] Short-term tapering in these studies occurred over a period of one to three weeks, depending on the specific study protocol. Of the papers using a short-term tapering protocol, only thioridazine was common to all, including second-generation antipsychotics included in the most recent study.[35] Three studies reported a mixed tapering strategy based on the dose of antipsychotic received.[38–40] If the antipsychotic received was lower than a defined antipsychotic dose, the medication was discontinued. If the dose received exceeded the threshold, patients were tapered over a period of one to three weeks, depending on the specific study protocol. Overall, no one tapering approach was common across the studies.

Four studies described interventions that did not have explicit protocols for tapering and discontinuing antipsychotics.[41–44] Three of the studies used educational interventions to reduce antipsychotic use, while one used a psychogeriatric rehabilitation program.[41–44] Of the three educational interventions, two provided staff-level educational programs to improve psychotropic medication use and included specific recommendations for tapering guidance, while one provided no specific tapering recommendations.[41–43] The psychogeriatric rehabilitation program had no explicit tapering guidance, but used a pharmacist to review participants' records to eliminate unnecessary psychopharmacologic medication and to reduce antipsychotics used in the intervention facility.[44]

Pharmacokinetic-Based Antipsychotic Tapering Recommendations

Based on the review of the pharmacokinetic information, recommended times for dose adjustments for commonly used medications currently on the market are provided for specific antipsychotics with second-generation antipsychotics shown in Table 1 and first-generation antipsychotics shown in Table 3. The time interval between dose reductions for second-generation antipsychotics in the pharmacokinetically based regimen ranged from as frequently as every two weeks to as long as every two months (Table 1). Assuming a stepwise progression from the first dose reduction and then a second dose reduction, with time for clinical evaluation and time to reach steady state after each, it would take at least two reductions prior to discontinuation. The estimated time to complete discontinuation ranges from four weeks to four months for second-generation antipsychotics and a minimum of four to eight weeks for first-generation antipsychotics. In the case of paliperidone, the times were further prolonged when adjusting for renal impairment (Table 1). For olanzapine, the recommended interval between dose reductions is two to four weeks, with an estimated time to discontinuation of four to eight weeks. Table 3 shows that the recommended intervals for dose reductions for first-generation antipsychotics were shorter and ranged from every two to four weeks.

Discussion

We found little evidence on which to base recommendations for discontinuation of off-label use of antipsychotics in older adults. The majority of trials (n = 4) included a fixed two-week tapering protocol, and a minority (n = 3) used abrupt discontinuation. Only three trials used a strategy where time-to-discontinuation was based on antipsychotic dose. Of the 10

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trials directly focusing on dose discontinuation, few were recent and tended to focus on second-generation antipsychotics in the tapering protocols. While a summary of these studies found little evidence for adverse drug-withdrawal effects overall in a combined analysis these studies were not powered to detect this outcome.[20] There were conflicting outcomes among the studies. Our analysis of specific pharmacokinetic information for individual second-generation and first-generation antipsychotics provided a theoretically based recommendation strategy. Our proposed pharmacokinetic-based calculations for tapering indicate that longer and more gradual reductions may be prudent. Protocols used in randomized trials were shorter than our theoretically based recommended tapering strategies.

Relatively little information is available to guide antipsychotic prescribing in elderly patients, and many of the drugs do not have published pharmacokinetic studies.[30] A comparison of the results of our theoretically based GDR strategy with formal pharmacokinetic evaluation studies provides evidence that our findings are consistent with empiric studies.[30] For example, Snoeck et al. confirmed that the half-life of the risperidone metabolite was longer in older adults than in younger individuals, and Ereshefsky et al. reported the elimination half-life of olanzapine to be 68% and 42% longer in elderly men and women, respectively, compared with young individuals.[46,47] One study of nine elderly individuals using quetiapine found that the elimination half-life was 6.2 to 6.8 hours and that clearance was reduced by about 50%.[48] While formal studies to validate each drug-elimination pattern would be ideal, they are expensive and difficult in the frail elderly population. This underscores the importance of our theoretical GDR strategy in the absence of more formal studies.

There are a number of considerations a prescriber must take into account before following these proposed guidelines. First, it is important to remember that tapering is not indicated in patients taking antipsychotics for FDA-approved uses like schizophrenia or Tourette's syndrome. Attempts to taper antipsychotics are also not recommended for patients who have a prior history of being a danger to themselves or others or if two prior taper attempts have failed.[12]

We acknowledge that slowly tapering antipsychotics will prolong the amount of time that a patient is on an antipsychotic and that observational data suggest that patients with prolonged antipsychotic exposure are known to have greater rates of mortality.[6–8,49] The clinical decision to abruptly stop or slowly taper should consider the amount of time that a patient has been on an antipsychotic and weigh the potential risks of continued exposure against the potential benefit of discontinuation. Abrupt discontinuation may be more appropriate when the patient newly initiates antipsychotics because previous research shows that the rate of mortality is highest within the first 30 to 40 days of initiation of therapy.[6,7,49] For long-term antipsychotic users, the rate of death is still higher than for nonusers (but lower than the first 30 to 40 days after initiation of therapy), but a gradual taper may be more successful in preventing relapse or withdrawal symptoms than abrupt discontinuation. While in practice it can be difficult for nursing facility staff or prescribers to determine how long each patient has received antipsychotics, estimated duration of therapy is important to consider in the clinical decision process on how rapidly to discontinue antipsychotics.[13]

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Given that up to 80% of patients with dementia experience BPSD, and the growing pressures to reduce the prevalence of off-label antipsychotic use in nursing facilities in the United States, rigorous studies of a more gradual tapering approach are warranted.[3,50] Empiric work is necessary to test the clinical effectiveness and feasibility of using these pharmacologically based tapering recommendations. For patients who do not meet any of the above exclusion criteria, further research is required to determine how factors like antipsychotic dose or duration of treatment might affect tapering strategy. It might be advisable to allow for longer periods of adjustment time at steady-state between taper intervals for those patients who have been on antipsychotics at a particularly high dose or for a long period of time. Tapering will require careful monitoring of all patients to determine whether behavior remains stable as the antipsychotics are slowly withdrawn.

Conclusion

Good clinical practice and federal regulations for nursing facility care call for the removal of unnecessary drugs in all nursing facility residents.[11] We suggest that a pharmacologically based protocol for tapering be considered when attempting GDRs. While further study is needed to garner evidence for whether such an approach reduces the incidence of recurrent neuropsychiatric symptoms, it remains clear that current strategies used for tapering older patients off of antipsychotics are unstandardized, not validated, and need to be addressed.

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ABBREVIATIONS:

BPSD	Behavioral and psychological symptoms of dementia
FDA	Food and Drug Administration
GDR	Gradual dose reduction
OBRA	Omnibus Budget Reconciliation Act of 1987

References

1. Briesacher BA, Tjia J, Field T et al. Antipsychotic use among nursing facility residents. JAMA 2013;309:440–2. [PubMed: 23385262]
2. U.S. Department of Health and Human Services, Office of Inspector General. Medicare atypical antipsychotic drug claims for elderly nursing facility residents. Washington, DC: US Department of Health and Human Services; 2011 5. Reprint no.: OEI-07-08-00150.
3. Lyketsos CG, Lopez O, Jones B et al. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the Cardiovascular Health Study. JAMA 2002;288:1475–83. [PubMed: 12243634]

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4. U.S. Food and Drug Administration. Public Health Advisory: deaths with antipsychotics in elderly patients with behavioral disturbances. Available at http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm053171. Accessed November 7, 2014.
5. U.S. Food and Drug Administration. Information for healthcare professionals: conventional antipsychotics. Available at http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm124830. Accessed November 7, 2014.
6. Gill SS, Bronskill SE, Normand SL et al. Antipsychotic drug use and mortality in older adults with dementia. Ann Intern Med 2007;146:775–86. [PubMed: 17548409]
7. Schneeweiss S, Setoguchi S, Brookhart A et al. Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. CMAJ 2007;176:627–32. [PubMed: 17325327]
8. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2012;60:616–31. [PubMed: 22376048]
9. Sink KM, Holden KF, Yaffe K. Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. JAMA 2005;293:596–608. [PubMed: 15687315]
10. Franco KN, Messinger-Rapport B. Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. J Am Med Dir Assoc 2006;7:201–2. [PubMed: 16503315]
11. Omnibus Budget Reconciliation Act of 1987: Subtitle C. Nursing facility reform: PL100–203. Washington, DC: National Coalition for Nursing Facility Reform; 1987.
12. Centers for Medicare & Medicaid Services. State Operations Manual: Appendix PP – guidance to surveyors for long term care facilities, F329. Available at http://cms.hhs.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/som107ap_pp_guidelines_ltcf.pdf. Accessed April 5, 2015.
13. Bonner A, Field T, Lemay C et al. Rationales that providers and family members cited for the use of antipsychotic medications in nursing facility residents with dementia. J Am Geriatr Soc 2015; 63:302–8. [PubMed: 25643635]
14. Gerety MB, Cornell JE, Plichta DT et al. Adverse events related to drugs and drug withdrawal in nursing facility residents. J Am Geriatr Soc 1993;41:1326–32. [PubMed: 8227915]
15. Graves T, Hanlon JT, Schmader KE et al. Adverse events after discontinuing medications in elderly outpatients. Arch Intern Med 1997;157:2205–10. [PubMed: 9342997]
16. Bain KT, Holmes HM, Beers MH et al. Discontinuing medications: a novel approach for revising the prescribing stage of the medication-use process. J Am Geriatr Soc 2008;56:1946–52. [PubMed: 18771457]
17. Hanlon JT, Handler SM, Maher RL et al. Geriatric pharmacotherapy and polypharmacy. In Fillit HM, Rockwood K, Woodhouse K, eds. Brocklehurst's Textbook of Geriatric Medicine and Gerontology. 7th ed. London, UK: Churchill Livingston; 2012: 880–5.
18. Ashton H The diagnosis and management of benzodiazepine dependence. Curr Opin Psychiatry 2005;18:249–55. [PubMed: 16639148]
19. Viguera AC, Baldessarini RJ, Hegarty JD et al. Clinical risk following abrupt and gradual withdrawal of maintenance neuroleptic treatment. Arch Gen Psychiatry 1997;54:49–55. [PubMed: 9006400]
20. Declercq T, Petrovic M, Azermai M et al. Withdrawal versus continuation of chronic antipsychotic drugs for behavioural and psychological symptoms in older people with dementia. Cochrane Database Syst Rev 2013:CD007726. [PubMed: 23543555]
21. Mita Y, Akishita M, Tanaka K et al. Improvement of inappropriate prescribing and adverse drug withdrawal events after admission to long-term care facilities. Geriatr Gerontol Int 2004;4:146–50.
22. de Leon J, Stanilla JK, White AO et al. Anticholinergics to treat clozapine withdrawal. J Clin Psychiatry 1994;55:119–20. [PubMed: 8071251]
23. Kohen I, Kremen N. A case report of quetiapine withdrawal syndrome in a geriatric patient. World J Biol Psychiatry 2009;10:985–6. [PubMed: 17965985]
24. Ballard C, Lana MM, Theodoulou M, et al. A randomised, blinded, placebo-controlled trial in dementia patients continuing or stopping neuroleptics (the DART-AD trial). PLoS Med 2008;5:e76. [PubMed: 18384230]

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25. Reidenberg MM. Drug discontinuation effects are part of the pharmacology of a drug. J Pharmacol Exp Ther 2011;339:324–8. [PubMed: 21849624]
26. Brunton LL, Chabner BA, Knollman B. Goodman and Gilman's Pharmacological Basis of Therapeutics. 12th ed. New York, NY: McGraw-Hill Medical; 2011.
27. Hutchison LC, O'Brien CE. Changes in pharmacokinetics and pharmacodynamics in the elderly patient. J Pharm Pract 2007;20:4–12.
28. Miller SW. Therapeutic drug monitoring in the geriatric patient. In: Murphy JE, editor. Clinical Pharmacokinetics. Bethesda, MD: American Society of Health-System Pharmacists; 2007. pp 391–401.
29. Wooten JM. Pharmacotherapy considerations in elderly adults. South Med J 2012;105:437–45. [PubMed: 22864103]
30. Sweet RA, Pollock BG. New atypical antipsychotics. Experience and utility in the elderly. Drugs Aging 1998;12:15–27. [PubMed: 9673862]
31. Mauri MC, Volonteri LS, Colasanti A et al. Clinical pharmacokinetics of atypical antipsychotics: a critical review of the relationship between plasma concentrations and clinical response. Clin Pharmacokinet 2007; 46:359–88. [PubMed: 17465637]
32. Hiemke C, Baumann P, Bergemann N et al. AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011. Pharmacopsychiatry 2011;44:195–235.
33. Findlay D, Sharma J, McEwen J et al. Double-blind controlled withdrawal of thioridazine treatment in elderly female inpatients with senile dementia. Int J Geriatr Psychiatry 1989;4:115–20.
34. Cohen-Mansfield J, Lipson S, Werner P et al. Withdrawal of haloperidol, thioridazine, and lorazepam in the nursing facility: a controlled, double-blind study. Arch Intern Med 1999;159:1733–40. [PubMed: 10448776]
35. van Reekum R, Clarke D, Conn D et al. A randomized, placebo-controlled trial of the discontinuation of long-term antipsychotics in dementia. Int Psychogeriatr 2002;14:197–210. [PubMed: 12243210]
36. Ballard CG, Thomas A, Fossey J et al. A 3-month, randomized, placebo-controlled, neuroleptic discontinuation study in 100 people with dementia: the neuropsychiatric inventory median cutoff is a predictor of clinical outcome. J Clin Psychiatry 2004;65:114–9. [PubMed: 14744180]
37. Ruths S, Straand J, Nygaard HA et al. Stopping antipsychotic drug therapy in demented nursing facility patients: a randomized, placebo-controlled study--the Bergen District Nursing Facility Study (BEDNURS). Int J Geriatr Psychiatry 2008;23:889–95. [PubMed: 18306150]
38. Bridges-Parlet S, Knopman D, Steffes S. Withdrawal of neuroleptic medications from institutionalized dementia patients: results of a double-blind, baseline-treatment-controlled pilot study. J Geriatr Psychiatry Neurol 1997;10:119–26. [PubMed: 9322135]
39. Devanand DP, Pelton GH, Cunqueiro K et al. A 6-month, randomized, double-blind, placebo-controlled pilot discontinuation trial following response to haloperidol treatment of psychosis and agitation in Alzheimer's disease. Int J Geriatr Psychiatry 2011; 26:937–43. [PubMed: 21845596]
40. Devanand DP, Mintzer J, Schultz SK et al. Relapse risk after discontinuation of risperidone in Alzheimer's disease. N Engl J Med 2012;367:1497–507. [PubMed: 23075176]
41. Avorn J, Soumerai SB, Everitt DE et al. A randomized trial of a program to reduce the use of psychoactive drugs in nursing facilities. N Engl J Med 1992;327:168–73. [PubMed: 1608408]
42. Ray WA, Taylor JA, Meador KG et al. Reducing antipsychotic drug use in nursing facilities. A controlled trial of provider education. Arch Intern Med 1993;153:713–21. [PubMed: 8447709]
43. Monette J, Champoux N, Monette M et al. Effect of an interdisciplinary educational program on antipsychotic prescribing among nursing facility residents with dementia. Int J Geriatr Psychiatry 2008;23:574–9. [PubMed: 17968860]
44. Fitz D, Mallya A. Behavioral reactions to psychotropic medication changes for nursing facility residents receiving psychogeriatric programming. J Appl Gerontol 1990;9:194–210.
45. Horwitz GJ, Tariot PN, Mead K et al. Discontinuation of antipsychotics in nursing facility patients with dementia. Am J Geriatr Psychiatry 1995;3:290–9. [PubMed: 28531062]

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46. Snoeck E, Van Peer A, Sack M et al. Influence of age, renal and liver impairment on the pharmacokinetics of risperidone in man. Psychopharmacology 1995;122:223–9. [PubMed: 8748391]

47. Ereshefsky L. Pharmacokinetics and drug interactions: update for new antipsychotics. J Clin Psychiatry 1996;57:12–25.

48. Thyrum PT, Jaskiw G, Fuller M et al. Multiple-dose pharmacokinetics of ICI 204,636 in elderly patients with selected psychotic disorders. Psychopharmacol Bull 1996;32:524.

49. Wang PS, Schneeweiss S, Avorn J et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. N Engl J Med 2005;353:2335–41. [PubMed: 16319382]

50. Centers for Medicare & Medicaid Services. National Partnership to Improve Dementia Care exceeds goal to reduce use of antipsychotic medications in nursing facility: CMS announces new goal. 2014. Available at http://www.cms.gov/Newsroom/MediaReleaseDatabase/Press-releases/2014-Press-releases-items/2014-09-19.html. Accessed October 30, 2014.

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Table 1.

Suggested Tapering Schedule by Specific Drug: Second-Generation Antipsychotics

Generic/Brand	$t_{½}$	Adjusted $t_{½}$ for Increased Age (65–89 Yr: 1.5 × $t_{½}$)	Calculated Time to Steady-State (5–7 Half-Lives to Reach Steady State)	Time to Next Gradual Dose Reduction (Leave at Steady State for ~ 7 Days)	Clinically Recommended Time Between Gradual Dose Reduction	Estimated Time to Discontinuation
Aripiprazole/ Abilify	Parent: 75 hrs Active metabolite: 94 hrs	Parent: 83 hrs Active metabolite: 141 hrs	41 days (based on active metabolite)	48 days	2 months	4 months
Asenapine/ Saphris	Parent: 24 hrs	Parent: 36 hrs	8–12 days	15–19 days	3 weeks	6 weeks
Clozapine/ Clozaril	Parent: 8–12 hrs	Parent: 12–18 hrs	4–5 days	10.5–12 days	2 weeks	4 weeks
lloperidone/ Fanapt	Parent: 18–33 hrs P88: 26–37 hrs P95: 23–31 hrs	Parent: 27–40 hrs P88: 39–56 hrs P95: 35–47 hrs	Parent: 8–12 days P88: 11–16 days P95: 10–14 days	Parent: 15–19 days P88: 18–24 days P95: 17–21 days	3 weeks	6 weeks
Lurasidone/ Latuda	Parent: 18 hrs	Parent: 27 hrs	6–8 days	15 days	2 weeks	4 weeks
Olanzapine/ Zyprexa	Parent: 21–54 hrs	Parent: 32–81 hrs	9–24 days	16–31 days	2–4 weeks	4–8 weeks
Paliperidone/ lnvega	Parent: 23 hrs Renal impairment: 24–51 hrs	Parent: 35 hrs Renal impairment: 36–77 hrs	10 days Renal impairment: 11–22 days	17 days Renal impairment: 18–29 days	2 weeks Renal impairment: 3–4 weeks	4 weeks Renal impairment: 6–8 weeks
Quetiapine/ Seroquel	Parent: IR: 6 hrs ER: 7 hrs	Parent: IR: 9 hrs ER: 11 hrs	Parent: IR: 2.5 days ER: 3 days	Parent: IR: 9.5 days ER: 10 days	2 weeks	4 weeks
Risperidone/ Risperdal	Parent: 3–20 hrs Active metabolite: 21–30 hrs	Parent: 4–30 hrs Active metabolite: 32–45 hrs	Parent: 1–9 days Active metabolite: 9–13 days	Parent: 8–16 days Active metabolite: 16–20 days	2–3 weeks	4–6 weeks
Ziprasidone/ Geodon	Parent: 7 hrs	Parent: 11 hrs	Parent: 3 days	Parent: 10 days	2 weeks	4 weeks

Abbreviations: ER = Extended release, IR = Immediate release, P88, P95 = Active metabolite of iloperidone, $t_{½}$ = Drug half-life.

Source: Reference 26.

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Table 2.

Antipsychotic Tapering Regimens Published in Clinical Trials

Article	Tapering Protocol	Antipsychotics Included
Abrupt		
Bollard 2004[36]	No dose-reduction strategy	Chlorpromazine Haloperidol *Risperidone* Thioridazine Trifluoperazine
Bollard 2008[24]	No dose-reduction strategy	Chlorpromazine Haloperidol *Olanzapine* Promazine *Quetiapine* *Risperidone* Thioridazine Trifluoperazine
Ruths 2008[37]	No dose-reduction strategy	Haloperidol *Olanzapine* Risperidone
Short-Term		
Findlay 1989[33]	Dose tapered by 50% in week 1, and discontinued over the following week	Thioridazine
Horwitz 1995[45]	Dose tapered by 50% in week 1, tapered another 50% in week 2, and then discontinued	Haloperidol Perphenazine Molindone Thioridazine Thiothixene Trifluoperazine
Cohen-Mansfield 1999[34]	Dose tapered over a 3-week period	Haloperidol Thioridazine
Van Reekum 2002[35]	Dose tapered by 50% in week 1, tapered another 50% in week 2, and then discontinued	Haloperidol

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Article	Tapering Protocol	Antipsychotics Included
		Levomepromazine Loxapine *Olanzapine* *Risperidone* Thioridazine
Mixed-Strategy		
Bridges-Parlet 1997[38]	If baseline dose ≤ equivalent of 50 mg of chlorpromazine, medication abruptly discontinued. If baseline dose > equivalent of 50 mg of chlorpromazine, dose decreased by 50% in week 1 and then discontinued	Haloperidol Loxapine Mesoridazine Thioridazine Thiothixene Trifluoperazine
Devanand 2O11[39]	If baseline dose < 1 mg daily, medication abruptly discontinued. If baseline dose between 2–3 mg daily, dose decreased to 1 mg daily for 2 weeks and then discontinued. If baseline dose 4 mg daily, dose decreased by 50% in week 1, decreased 50% in week 2, and then discontinued	Haloperidol
Devanand 2012[40]	If baseline dose ≥ 2 mg daily, dose tapered over 1 week with a sequential double-blind substitution tapering period	*Risperidone*

Note: Italicized medications are second-generation antipsychotics.

Source: References 24, 33, 34, 36–40, 45.

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Table 3.

Suggested Tapering Schedule by Specific Drug: First-Generation Antipsychotics

Generic/Brand	$t_{½}$	Adjusted $t_{½}$ for Increased Age (65–89 Yr: 1.5 × $t_{½}$)	Calculated Time to Steady-State (5–7 days $t_{½}$ Reach Steady State)	Time to Next Gradual Dose Reduction (Leave at Steady State for ~ 7 Days)	Clinically Recommended Time Between Gradual Dose Reduction	Estimated Time to Discontinuation
Chlorpromazine/ Thorazine	24 hrs	36 hrs	- 10 days	- 17 days	3 weeks	6 weeks
Fluphenazine/Prolixin	18 hrs	27 hrs	- 8 days	- 15 days	2 weeks	4 weeks
Haloperidol/Haldol	18 hrs	27 hrs	- 8 days	- 15 days	2 weeks	4 weeks
Loxapine/Loxitane	Oral: 2–4 hrs	Oral: 3–6 hrs	Oral: 1–2 days	Oral: 8–9 days	2 weeks	4 weeks
Perphenazine/Trilafon	9–12 hrs	14–18 hrs	4–5 days	11–12 days	2 weeks	4 weeks
Pimozide/Orap	55 hrs	83 hrs	24 days	31 days	1 month	2 months
Prochlorperazine/Compro	Oral: 3–5 hrs IV: 7 hrs	Oral: 4–8 hrs IV: 11 hrs	Oral: 1–2 days IV: 3 days	Oral: 8–9 days IV: 10 days	2 weeks	4 weeks
Promethazine/Phenergan	5–14 hrs	8–21 hrs	2–6 days	9–13 days	2 weeks	4 weeks
Thioridazine/Mellaril	24 hrs	36 hrs	10 days	17 days	3 weeks	6 weeks
Thiothixene/Navane	34 hrs	51 hrs	15 days	23 days	3 weeks	6 weeks
Trifluoperazine/Stelazine	18 hrs	27 hrs	7 days	14 days	2 weeks	4 weeks

Abbreviations: IM = Intramuscular, IV = Intravenous, $t_{½}$ = Drug half-life.

Source: Reference 26.

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