SUPPLEMENTARY MATERIAL

Cohen D, Recalt A. Discontinuing psychotropic drugs from participants in randomized controlled trials: Systematic review. *Psychotherapy & Psychosomatics*. DOI: 10.1159/000496733

Table 1: Search strings for databases searches

MEDLINE: ("Substance Withdrawal Syndrome"[Mesh] OR "Withholding Treatment"[Mesh] OR discontinuation[TI] OR reduction[TI]) AND ("Anticonvulsants"[Mesh] OR "Antidepressive Agents"[Mesh] OR "Antimanic Agents"[Mesh] OR "Benzodiazepines"[Mesh] OR "Antipsychotic Agents"[Mesh] OR "Serotonin Uptake Inhibitors"[Mesh] OR "Central Nervous System Stimulants"[Mesh] OR "Placebos"[Mesh]) AND "humans"[MeSH]).
EMBASE: 'drug withdrawal'/mj OR 'treatment withdrawal'/mj OR 'drug dose reduction'/mj AND ('anticonvulsive agent'/de OR 'antidepressant agent'/de OR 'benzodiazepine'/de OR 'benzodiazepine derivative'/de OR 'diazepam'/de OR 'neuroleptic agent'/de OR 'placebo'/de OR 'serotonin uptake inhibitor'/de OR 'unclassified drug'/de)
PsycINFO: TI(taper* OR withdraw* OR detox* OR suspen* OR discontinu*) AND ALL(psychostimulant* OR stimulant* OR antidepress* OR antipsychotic* OR neuroleptic* OR anxiolytic* OR anticonvuls* OR antiepilept* OR "mood stabili*" OR antimanic* OR anticholinergic* OR antiparkinsonian) AND ALL(method OR systemat* OR procedure) NOT ALL(tobacco OR smoking OR nicotin* OR coffee OR caffeine OR alcohol OR opioid* OR opiate*)

Figure 1: Flow diagram of article search and selection

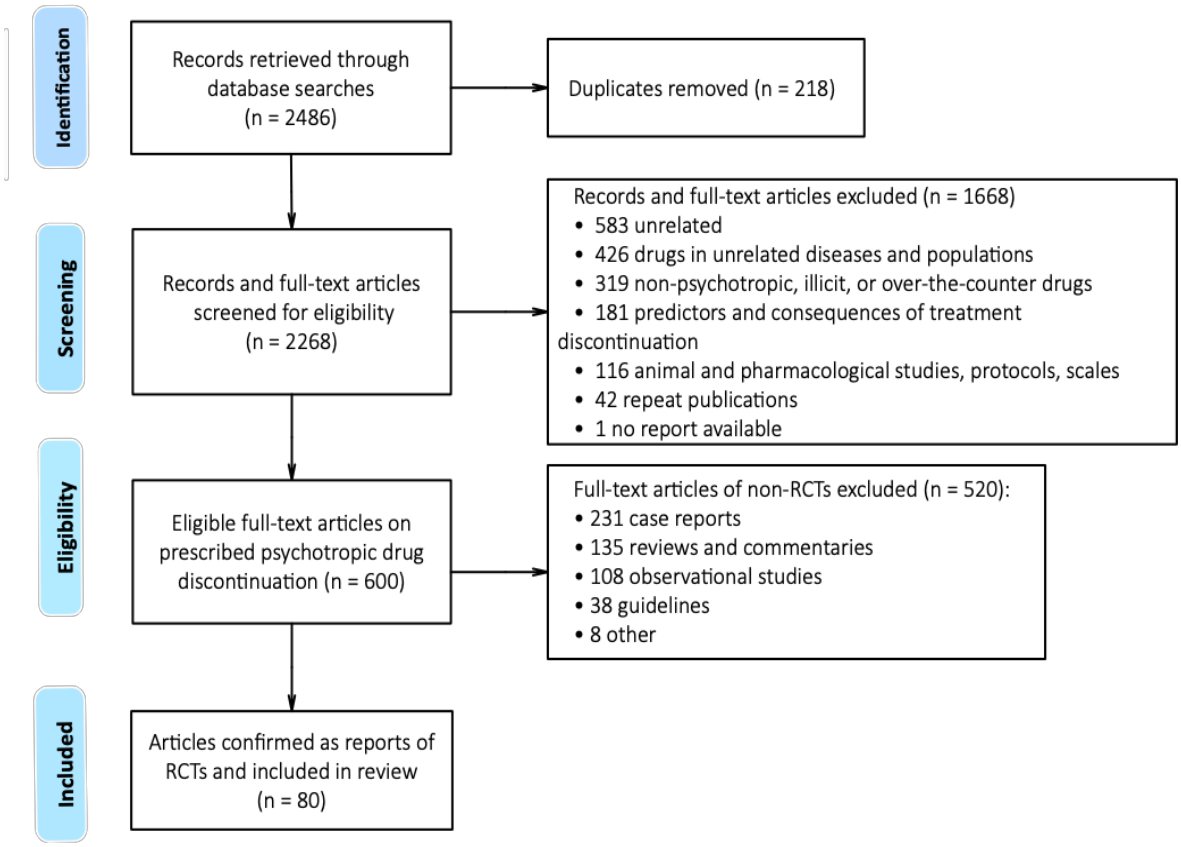


Table 2: List of the 80 RCTs included in review, with abridged justification or rationale for discontinuing psychotropic medications from participants

Reference	Abridged justification/rationale
Arnold LE, Lindsay RL, Conners CK et al: A double-blind, placebo-controlled withdrawal trial of dexmethylphenidate hydrochloride in children with attention deficit hyperactivity disorder. J Child Adolesc Psychopharmacol 2004;14:542–554.	Because d-MPH can suppress symptoms of a chronic illness, randomized withdrawal becomes a relapse prevention trial.
Baandrup L, Lindschou J, Winkel P et al: Prolonged-release melatonin versus placebo for benzodiazepine discontinuation in patients with schizophrenia or bipolar disorder: a randomised, placebo-controlled, blinded trial. World J Biol Psychiatry 2016;17:514–524.	BZDs are taken longer than indicated and produce adverse effects on all spheres of functioning; supplementary melatonin could facilitate discontinuation of BZDs.
Baillargeon L, Landreville P, Verreault R et al: Discontinuation of benzodiazepines among older insomniac adults treated with cognitive-behavioural therapy combined with gradual tapering: a randomized trial. Can Med Assoc J 2003;169:1015–1020.	To establish optimal support methods when withdrawing from harmful BZDs.
Baldwin DS, Cooper JA, Huusom AK, Hindmarch I: A double-blind, randomized, parallel-group, flexible-dose study to evaluate the tolerability, efficacy and effects of treatment discontinuation with escitalopram and paroxetine in patients with major depressive disorder. Int Clin Psychopharmacol 2006;21:159-169.	To evaluate tolerability (i.e., discontinuation or withdrawal effects) of SSRIs.
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 Psychiat 2004;65:114–119.	To overcome methodological limitations of previous trials of NLP discontinuation (i.e., not double blind or placebo controlled, not reflecting usual clinical practice, involving patients receiving atypical and typical NLPs).
Ballard CG, 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(4), e76.	To overcome methodological limitations of previous trials of NLP discontinuation (i.e., short duration).
Belleville G, Guay C, Guay B, Morin CM: Hypnotic taper with or without self-help treatment of insomnia: a randomized clinical trial J Consult Clin Psychol 2007;75:325–335.	Many BZD users become chronic and exposed to significant harm, and abrupt withdrawal from BZDs is associated with symptoms. Supervised gradual withdrawal can help users to completely discontinue and minimize withdrawal symptoms.
Bergh S, Selbaek G, Engedal K: Discontinuation of antidepressants in people with dementia and neuropsychiatryic symptoms (DESEP study): double blind, randomised, parallel group, placebo controlled trial. BMJ 2012;344, e1566.	To test the effects of withdrawing ADs in people with dementia since these drugs could be harmful to patients.
Brams M, Weisler R, Findling RL et al: Maintenance of efficacy of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder: randomized withdrawal design. J Clin Psychiatry 2012;73:977–983.	To overcome ethical ("withholding known effective treatment") and methodological (high dropout) issues in long-term placebo-controlled drug trials by using a shorter withdrawal design; to measure relapse in order to demonstrate maintenance of tx effects.
Buitelaar JK, Trott GE, Hofecker M et al: Long-term efficacy and safety outcomes with OROS-MPH in adults with ADHD. Int J Neuropsychopharmacol 2012;15:1–13.	To evaluate the maintenance of the effect/relapse prevention of MPH.
Chen EY, Hui CL, Lam MM et al: Maintenance treatment with quetiapine versus discontinuation after one year of treatment in patients with remitted first episode psychosis: randomised controlled trial. BMJ 2010;341, c4024	To provide randomized, placebo-controlled data on decisions and guidelines to withdraw APs from stable first-episode patients.
Coghill DR, Banaschewski T, Lecendreux M et al: Maintenance of efficacy of lisdexamfetamine dimesylate in children and adolescents with attention-deficit/hyperactivity disorder: randomized-withdrawal study design. J Am Acad Child Adolesc Psychiatry 2014;53:647–57.	To overcome ethical and clinical issues in long-term placebo-controlled drug trials by using a randomized withdrawal design.
Cortese L, Caligiuri MP, Williams R et al: Reduction in neuroleptic-induced movement disorders after a switch to quetiapine in patients with schizophrenia. J Clin Psychopharmacol 2008;28:69–73.	More empirical support is needed to guide clinicians when switching APs.
Curran HV, Collins R, Fletcher S et al: Older adults and withdrawal from benzodiazepine hypnotics in general practice: effects on cognitive function, sleep, mood and quality of life. Psychol Med 2003;33:1223–1237.	To determine whether withdrawal from BZDs reverses drug-induced impairment.
de Kuijper G, Evenhuis H, Minderaa RB, Hoekstra PJ: Effects of controlled discontinuation of long-term used antipsychotics for behavioural symptoms in individuals with intellectual disability. J Intellect Disabil Res 2014;58:71–83.	To investigate effects on behavior of controlled discontinuation from APs, given these drugs' potentially harmful effects in patients with ID.

Dell'Osso B, Hadley S, Allen A et al: Escitalopram in the treatment of impulsive-compulsive internet usage disorder: an open-label trial followed by a double-blind discontinuation phase. J Clin Psychiatry 2008; 69:452–456.	None found.
Devanand DP, Mintzer J, Schultz SK et al: Relapse risk after discontinuation of risperidone in Alzheimer's disease. NEJM 2012;367:1497–1507.	To evaluate relapse prevention in AP treatment by means of a randomized withdrawal design.
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;26:937–943.	To overcome limitations (unclear indication for prescription, unknown response to drug, multiple APs discontinued) of previous relapse-prevention discontinuation trials of APs.
Emsley R, Chiliza B, Asmal L et al: A randomized, controlled trial of omega-3 fatty acids plus an antioxidant for relapse prevention after antipsychotic discontinuation in first-episode schizophrenia. Schizophr Res 2014;158:230–235.	Given risks of long-term exposure to APs, safe and tolerable alternative that could prevent relapse would be a major advance in the maintenance tx of schizophrenia.
Findling RL, Chang K, Robb A et al: Adjunctive maintenance lamotrigine for pediatric bipolar I disorder: a placebo-controlled, randomized withdrawal study. J Am Acad Child Adolesc Psychiatry 2015;54:1020-1031.	To overcome ethical and clinical issues in long-term placebo-controlled drug trials by using a randomized withdrawal design.
Ganguli R, Brar JS, Mahmoud R et al: Assessment of strategies for switching patients from olanzapine to risperidone: a randomized, open-label, rater-blinded study. BMC Med 2008;6:17.	To switch to a new AP when the current one shows lack of effectiveness.
Garzon C, Guerrero JM, Aramburu O, Guzman T: Effect of melatonin administration on sleep, behavioral disorders and hypnotic drug discontinuation in the elderly: a randomized, double-blind, placebo-controlled study. Aging Clin Exp Res 2009;21:38–43.	Discontinuing BZDs and treating sleep disorders with melatonin could improve sleep.
Ghaemi SN, Ostacher MM, El-Mallakh RS et al: Antidepressant discontinuation in bipolar depression: a Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) randomized clinical trial of long-term effectiveness and safety. J Clin Psychiatry 2010;71:372–380.	None found.
Goodwin GM, Emsley R, Rembry S, Rouillon F: Agomelatine prevents relapse in patients with major depressive disorder without evidence of a discontinuation syndrome: A 24-week randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2009;70:1128–1137.	A relapse-prevention trial of an AD without marked potential for withdrawal symptoms is valuable in long-term treatment effectiveness research.
Gorenstein EE, Kleber MS, Mohlman J et al: Cognitive-behavioral therapy for management of anxiety and medication taper in older adults. Am J Geriatr Psychiatry 2005;13:901–909.	To assist in reducing the use of ineffective anti-anxiety medication in younger adults with panic disorder.
Grant JE, Potenza MN: Escitalopram treatment of pathological gambling with co-occurring anxiety: an open-label pilot study with double-blind discontinuation. Int Clin Psychopharmacol 2005;21:203–209.	None found.
Haessler F, Glaser T, Beneke M et al: Zuclopenthixol Disruptive Behaviour Study Group: Zuclopenthixol in adults with intellectual disabilities and aggressive behaviours: discontinuation study. Br J Psychiatry 2007;190:447–448.	To conduct a RCT of the medication.
Hartford J, Kornstein S, Liebowitz M et al: Duloxetine as an SNRI treatment for generalized anxiety disorder: results from a placebo and active-controlled trial. Int Clin Psychopharmacol 2007;22:167–174.	None found.
Huijbers MJ, Spinhoven P, Spijker J et al: Discontinuation of antidepressant medication after mindfulness-based cognitive therapy for recurrent depression: Randomised controlled non-inferiority trial. Br J Psychiatry 2016; 10.1192/bjp.bp.115.168971	To test a psychosocial alternative to drug treatment of depression after drug treatment has been discontinued.
Judge R, Parry MG, Quail D, Jacobson JG: Discontinuation symptoms: comparison of brief interruption in fluoxetine and paroxetine treatment. Int Clin Psychopharmacol 2002;17:217–225.	Missed doses occur often in real life. To examine the effects of an abrupt, brief interruption of SSRIs.
Kafantaris V, Coletti DJ, Dicker R et al: Lithium treatment of acute mania in adolescents: a placebo-controlled discontinuation study. J Am Acad Child Adolesc Psychiatry 2004;43:984–993.	To overcome ethical and feasibility issues in traditional placebo-controlled, parallel group clinical trials of lithium.
Kasper S, Iglesias-Garcia C, Schweizer E et al: Pregabalin long-term treatment and assessment of discontinuation in patients with generalized anxiety disorder. Int J Neuropsychopharmacol 2014; 17:685-695.	To evaluate discontinuation effects of pregabalin and to test the maintenance of its treatment effect following discontinuation.
Kennedy SH, Giacobbe P, Placenza F et al: Depression treatment by withdrawal of short-term low-dose antipsychotic, a proof-of-concept randomized double-blind study. J Affect Dis 2014;166:139–143.	To use a drug withdrawal-induced neuronal state (dopamine supersensitivity) as a possible treatment for depressive symptoms.
Khan A, Musgnung J, Ramey T et al: Abrupt discontinuation compared with a 1-week taper regimen in depressed outpatients treated for 24 weeks with desvenlafaxine 50 mg/d. J Clin Psychopharmacol 2014; 34:365–368.	To compare two discontinuation methods of desvenlafaxine on their associated withdrawal symptoms.

Koran LM, Aboujaoude EN, Gamel NN: Escitalopram treatment of kleptomania: an open-label trial followed by double-blind discontinuation. J Clin Psychiatry 2007a;68:422–427.	To distinguish a placebo response to an AD from a true drug effect.
Koran LM, Aboujaoude EN, Solvason B et al: Escitalopram for compulsive buying disorder: a double-blind discontinuation study. J Clin Psychopharmacol 2007b;27:225-227.	To distinguish a placebo response to an AD from a true drug effect.
Koran LM, Chuong HW, Bullock KD, Smith SC: Citalopram for compulsive shopping disorder: an open-label study followed by double-blind discontinuation. J Clin Psychiatry 2003;64:793–798.	None found.
Koran LM, Gamel NN, Choung HW et al: Mirtazapine for obsessive-compulsive disorder: an open trial followed by double-blind discontinuation. J Clin Psychiatry 2005; 66:515–520.	None found.
Krystal A, Fava M, Rubens R et al: Evaluation of eszopiclone discontinuation after cotherapy with fluoxetine for insomnia with coexisting depression. J Clin Sleep Med 2007;3:48–55.	To examine the effects of abruptly discontinuing eszopiclone.
Kudoh A, Katagai H, Takase H, Takazawa T: Effect of preoperative discontinuation of antipsychotics in schizophrenic patients on outcome during and after anaesthesia. Eur J Anaesthesiol 2004;21–412–420.	To add to the evidence base about effects of discontinuing APs on perioperative outcomes.
Lee C-T, Conde BJL, Mazlan M et al: Switching to olanzapine from previous antipsychotics: A regional collaborative multicenter trial assessing 2 switching techniques in Asia Pacific. J Clin Psychiatry 2002;63:569–576.	To characterize the efficacy and safety of olanzapine in Asian patients.
Lemoine P, Kermadi I, Garcia-Acosta S et al: Double-blind, comparative study of cyamemazine vs. bromazepam in the benzodiazepine withdrawal syndrome. Progr Neuro-psychopharmacol Biol Psychiatry 2006;30:131–137.	To reduce withdrawal reactions when discontinuing BZDs by adding the AP cyamemazine.
Mavissakalian MR, Perel JM: 2nd year maintenance and discontinuation of imipramine in panic disorder with agoraphobia. Ann Clin Psychiatry 2001;13:63–67.	To explore the potentially protective effects of long-term maintenance AD treatment.
Mayur PM, Gangadhar BN, Subbakrishna DK, Janakiramaiah N: Discontinuation of antidepressant drugs during electroconvulsive therapy: a controlled study. J Affect Dis 2000;58:37–41.	With no systematic research and conflicting recommendations, need to determine benefits and risks of continuing ADs during ECT.
Mercier-Guyon C, Chabannes JP, Saviuc P: The role of captodiamine in the withdrawal from long-term benzodiazepine treatment. Curr Med Res Opin 2004;20:1347–1355.	To facilitate discontinuation of BZDs by patients who no longer benefit from these drugs.
Montgomery SA, Kennedy SH, Burrows GD et al: Absence of discontinuation symptoms with agomelatine and occurrence of discontinuation symptoms with paroxetine: a randomized, double-blind, placebo-controlled discontinuation study. Int Clin Psychopharmacol 2004;19:271–280.	To overcome methodological limitations of previous investigations of discontinuation effects of ADs by using double-blind randomized discontinuation.
Morin CM, Bastien C, Guay B et al: Randomized clinical trial of supervised tapering and cognitive behavior therapy to facilitate benzodiazepine discontinuation in older adults with chronic insomnia. Am J Psychiatry 2004;161:332–342.	BZDs have harmful effects and are used for longer periods than indicated, especially by older adults with sleep, psychological, and chronic medical problems.
Mueser KT, Sengupta A, Schooler NR et al: Family treatment and medication dosage reduction in schizophrenia: effects on patient social functioning, family attitudes, and burden. J Consult Clin Psychol 2001;61:3–12.	To investigate the effects of different strategies of family support and medication management on social functioning of patients with schizophrenia.
Nakao M, Takeuchi T, Nomura K et al: Clinical application of paroxetine for tapering benzodiazepine use in non-major-depressive outpatients visiting an internal medicine clinic. Psychiatry Clin Neurosci 2006;60:605–610.	To determine whether SSRIs can help patients discontinue high-potency BZDs more likely to cause abuse and dependency.
O'Connor K, Marchand A, Brousseau L et al: Cognitive-behavioural, pharmacological and psychosocial predictors of outcome during tapered discontinuation of benzodiazepines. Clin Psychol Psychother 2008;15:1–14.	None found.
Otto MW, McHugh RK, Simon NM et al: Efficacy of CBT for benzodiazepine discontinuation in patients with panic disorder: Further evaluation. Behav Res Ther	Abrupt and gradual withdrawal of BZDs are both associated with withdrawal and rebound anxiety and relapse of panic disorder.
Pae C-U, Serretti A, Chiesa A et al: Immediate versus gradual suspension of previous treatments during switch to aripiprazole: Results of a randomized, open label study. Eur Neuropsychopharmacol 2009;19:562–570.	To provide evidence from controlled studies about whether to withdraw a current AP abruptly or gradually when switching to aripiprazole.
Petrovic M, Pevernagie D, Mariman A et al: Fast withdrawal from benzodiazepines in geriatric inpatients: a randomised double-blind, placebo-controlled trial. J Clin Psychol 2002;57:759–764.-	BZD-produced impairments reverse upon discontinuation, hence supervised withdrawal from BZDs should be considered whenever possible.
Research Units on Pediatric Psychopharmacology Autism Network. Risperidone treatment of autistic disorder: longer-term benefits and blinded discontinuation after 6 months. Am J Psychiatry 2005;162:1361–1369.	To determine whether observed positive short-term effects of risperidone would endure over time.

Rickels K, DeMartinis N, García-España, F et al: Imipramine and buspirone in treatment of patients with generalized anxiety disorder who are discontinuing long-term benzodiazepine therapy. Am J Psychiatry 2000;157:1973–1979.	Achieving successful BZD discontinuation after prolonged treatment is often difficult.
Ristanovic RK, Liang H, Hornfeldt CS, Lai C: Exacerbation of cataplexy following gradual withdrawal of antidepressants: manifestation of probable protracted rebound cataplexy. Sleep Med 2009;10:416–421.	No systematic study of discontinuation of anti-cataplectic ADs has been conducted on a large sample of patients with narcolepsy.
Roehrs TA, Randall S, Harris E, Maan R, Roth T: Twelve months of nightly zolpidem does not lead to rebound insomnia or withdrawal symptoms: a prospective placebo-controlled study. Sleep 2012;26:1088–1095.	To determine whether rebound insomnia will develop into a complete withdrawal syndrome after discontinuing chronic BZD use.
Ruths S, Straand J, Nygaard HA, Aarsland D: Stopping antipsychotic drug therapy in demented nursing home patients: a randomized, placebo-controlled study–the Bergen District Nursing Home Study (BEDNURS). Int J Ger Psychiatry 2008;23:889–895.	Careful AP withdrawal is essential to establish current treatment effectiveness, but health outcomes of such withdrawal are scarcely documented.
Saksa JR, Baker CB, Woods SW: Mood-stabilizer-maintained, remitted bipolar patients: taper and discontinuation of adjunctive antipsychotic medication. Gen Hosp Psychiatry 2004;26:233–236.	To determine in bipolar patients clinical outcomes associated with randomization to adjunctive AP continuation versus discontinuation.
Sandler AD, Glesne CE, Bodfish JW: Conditioned placebo dose reduction: a new treatment in attention-deficit hyperactivity disorder? J Dev Behav Pediatr 2010;31:369–375.	To determine the lowest effective doses of stimulant medication for children.
Schmidt NB, Wollaway-Bickel K, Trakowski JH et al: Antidepressant discontinuation in the context of cognitive behavioral treatment for panic disorder. Behav Res Ther 2002;40:67–73.	No trials have evaluated whether CBT may assist PD patients discontinue ADs.
Sunder KR, Wisner KL, Hanusa BH, Perel JM: Postpartum depression recurrence versus discontinuation syndrome: observations from a randomized controlled trial. J Clin Psychiatry 2004;65:1266–1268.	To distinguish a withdrawal syndrome from a recurrence of MDD.
Swanson JM, Greenhill LL, Lopez FA et al: Modafinil film-coated tablets in children and adolescents with attention-deficit/hyperactivity disorder: results of a randomized, double-blind, placebo-controlled, fixed-dose study followed by abrupt discontinuation. J Clin Psychiatry 2006;67:137–147.	To evaluate the effects of abrupt discontinuation of stimulants for ADHD, as missed stimulant doses may lead to worsening behavior due to rapid efficacy loss.
Takeuchi H, Suzuki T, Remington G et al: Effects of risperidone and olanzapine dose reduction on cognitive function in stable patients with schizophrenia: an open-Label, randomized, controlled, pilot study. Schizophr Bull 2013;39:993–998.	To determine whether AP dose reduction reduces AP-related cognitive impairment.
Tandon R, Cucchiaro J, Phillips D et al: A double-blind, placebo-controlled, randomized withdrawal study of lurasidone for the maintenance of efficacy in patients with schizophrenia. J Psychopharmacol 2016;30:69–77.	To test lurasidone in preventing relapse in patients who are clinically stable on the drug.
Tint A, Haddad PM, Anderson IM: The effect of rate of antidepressant tapering on the incidence of discontinuation symptoms: a randomised study. J Psychopharmacol 2008;22:330–332.	To compare two strategies of discontinuing ADs.
Troost P, Lahuis BP, Steenhuis M-P et al: Long-term effects of risperidone in children with autism spectrum disorders: a placebo discontinuation study. J Am Acad Child Adolesc Psychiatry 2005;44:1137–1144.	To overcome ethical issues in long-term placebo-controlled RCTs of APs.
Ulfvarson J, Adami J, Wredling R et al: Controlled withdrawal of selective serotonin reuptake inhibitor drugs in elderly patients in nursing homes with no indication of depression. Eur J Clin Pharmacol 2003;59:735–740.	To study the effect of removing SSRIs in nursing home patients who have no documented indication for SSRIs or depression symptoms.
Vaishnavi S, Gadde K, Alamy S, Zhang W, Connor K, Davidson JR: Modafinil for atypical depression: effects of open-label and double-blind discontinuation treatment. J Clin Psychopharmacol 2006;26:373–378.	To test modafinil's efficacy in relapse prevention by means of a double-blind, placebo-controlled design.
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.	To document the effects of discontinuing APs, potentially harmful drugs used with dementia patients, by conducting a study with better methodology than previous studies.
Vicens C, Fiol F, Llobera J et al: Withdrawal from long-term benzodiazepine use: randomised trial in family practice. Br J Gen Pract 2006; 56, 958–963.	BZDs are harmful in long-term use and withdrawal from BZDs is difficult.
Vicens C, Bejarano F, Sempere E et al: Comparative efficacy of two interventions to discontinue long-term benzodiazepine use: cluster randomised controlled trial in primary care. Br J Psychiatry 2014;204:1–9.	There are adverse health outcomes of widespread long-term BZD use. Need to develop strategies to reduce the extent of BZD use.
Vissers FH, Knipschild PG, Crebolder HF: Is melatonin helpful in stopping the long-term use of hypnotics? A discontinuation trial. Pharm World Sci 2007;29:641–646.	To test melatonin or placebo in helping people discontinue chronic BZD use.
Vöhringer PA, Ostacher MJ, El-Mallakh RS et al: Antidepressants in type II versus type I bipolar depression: a randomized discontinuation trial. J Clin Psychopharmacol 2015;35:605–608.	None found.

Volavka J, Cooper TB, Czobor P et al: High-dose treatment with haloperidol: the effect of dose reduction. J Clin Psychopharmacol 2000;20:252–256.	To determine whether high doses of NLPs were really justified or necessary.
Voshaar RCO, Gorgels WJ, Mol AJ et al: Tapering off long-term benzodiazepine use with or without group cognitive-behavioural therapy: three-condition, randomised controlled trial. Br J Psychiatry 2003;182:498–504.	To overcome limitations of evaluations of previous BZD withdrawal programs (i.e., no control nonintervention).
Weisler R, Joyce JM, McGill L et al: Extended release quetiapine fumarate monotherapy for major depressive disorder: results of a double-blind, randomized, placebo-controlled study. CNS Spectr 2009;14:299–313.	None found.
Zahir A, Fraser W, Kerr MP et al: Reducing antipsychotic medication in people with a learning disability. Br J Psychiatry 2000;176:42–46.	Given questionable effectiveness of APs, need to overcome methodological limitations of previous studies to determine the feasibility of antipsychotic drug reduction.
Zarate CA Jr, Tohen M: Double-blind comparison of the continued use of antipsychotic treatment versus its discontinuation in remitted manic patients. Am J Psychiatry 2004;1161:169–71.	To determine benefits of lithium treatment following remission from acute mania.
Zitman FG, Couvee JE: Chronic benzodiazepine use in general practice patients with depression: an evaluation of controlled treatment and taper-off: report on behalf of the Dutch Chronic Benzodiazepine Working Group. Br J Psychiatry 2001;178:317–324.	To test a BZD discontinuation program in an unstudied patient subgroup, chronic BZD users suffering from depression.

Table 3: Discontinuation and supervision strategies employed

Discontinuation (n=78 RCTs[a])	Number of RCTs[b]	%
Fixed: taper during a set time period (n=14) with set dose reductions (n=1), or both (n=20)	35	44.9
Abrupt: immediate switch to placebo/no drug (as sole strategy, n=23, supplemented with conventional drug, n=2)	25	32.0
Flexible (n=11) or symptom-guided (n=1): timing and doses may be altered by participant	12	15.4
Supplemented with psychotropic drug: conventional (n=7) or complementary/alternative (n=3)	10	12.8
Supplemented with psychotherapy (individual, group, both [n=2 each]) and relaxation training (n=1)	7	9.0
Supplemented with education to patients (n=2) or clinicians (n=1): information packets and/or face-to face sessions with researchers	3	3.8
Supervision (n=73 RCTs[a])		
Supervised: controlled by researchers, doses provided and/or monitored	55	75.3
Guided: researchers provide guidelines with regular check-ins (n=14) or outside clinicians/ pharmacists who implement the discontinuation (n=2)	16	21.9
Unsupervised: researchers may or may not provide guidelines and do not check in with participants, who discontinue independently	2	2.7

Notes:
a. Two RCTs provided no information on discontinuation strategy and 7 provided no information on supervision.
b. Total and percentage for discontinuation strategies are greater than 78 and 100% as 13 RCTs used 2 strategies and 2 RCTs used 3 and 4 strategies concurrently.

Table 4: Justifications provided for gradual or abrupt discontinuation strategies

RCTs with two or more steps in discontinuation (n=54)		RCTs with abrupt discontinuation (n=23)		RCTs with both (n=3)	
No justification	31 (57.4%)	No justification	18 (78.2%)	No justification	2 (66.6%)
One or two sources cited, based on previous work by investigators, developed by experts	9	Justified because patients are taking small doses	2	Based on previous work by investigators	1
To prevent or minimize withdrawal syndromes, which may compromise blinding (n=1)	5	Best method to induce rebound insomnia	1		
To prevent clinical deterioration or for safety	3	Rarely investigated	1		
Gradual withdrawal takes drug half-life into account	2	Mimics interruptions in real life	1		
Determined by clinicians and varying according to patients' readiness to discontinue, and presence of withdrawal symptoms	2				
Mimics non-compliance in real life, slow tapering most common in clinical practice	2				

Figure 2: Duration of previous treatment prior to discontinuation, by antidepressant, antipsychotic, benzodiazepine, and stimulant RCT (n=68)

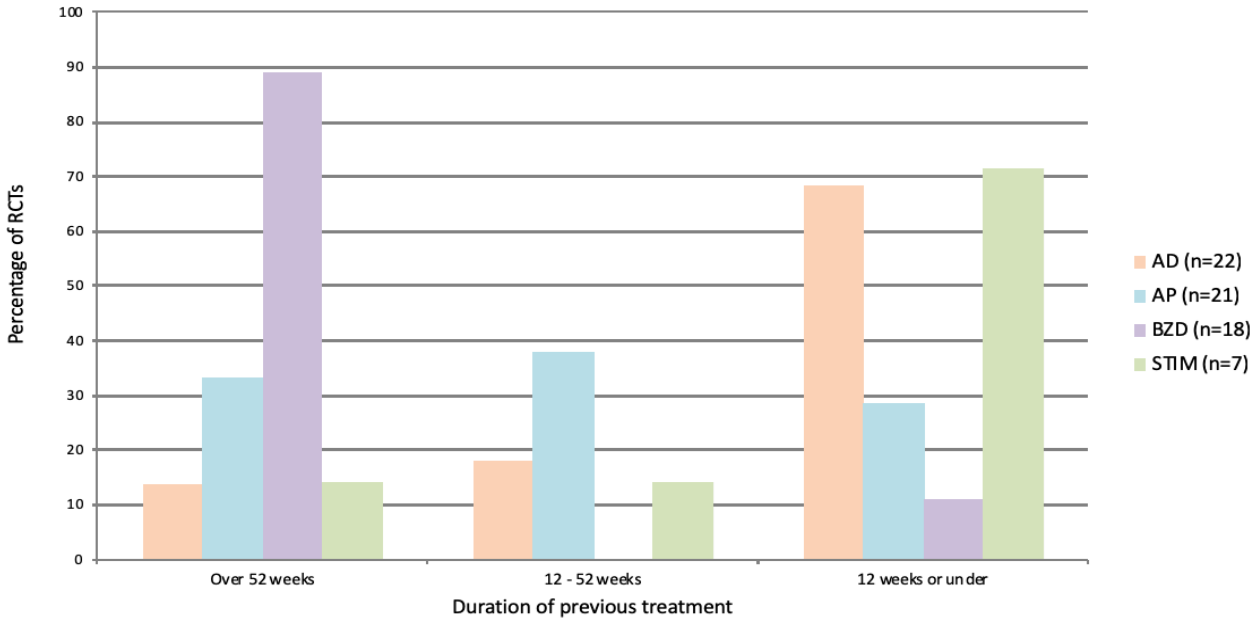
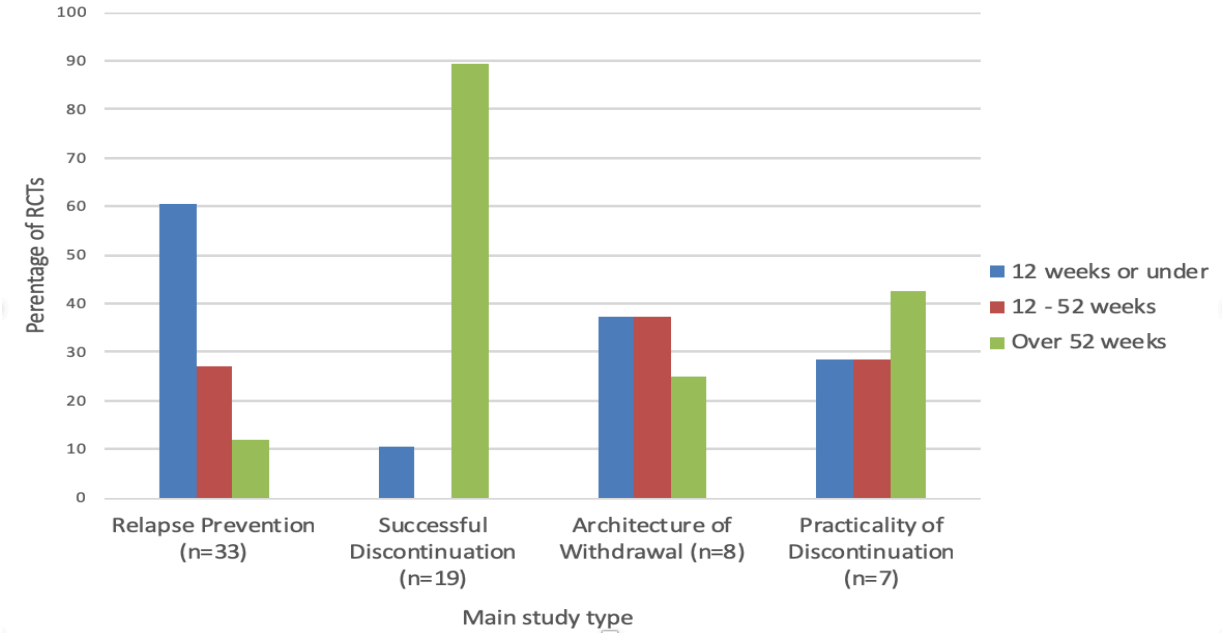


Figure 3: Duration of previous treatment prior to discontinuation, by main study type[1] (n=67)



Note to Figure 4: 1. The 4 main study types and 3 other minor types are described in Table 2 in the article. 13 RCTs did not provide information on previous medication history. In most Relapse-Prevention RCTs, only duration of the studies' open-label phase prior to discontinuation were given; durations ranged from 3 weeks to 76 weeks, with 1 outlier of "2-3 years." In Successful Discontinuation RCTs, stated durations ranged from "under 30 days" to "an average of 19.3 years." In Architecture of Withdrawal RCTs, stated durations ranged from 8 weeks to 14.0±7.9 years. In Practicality of Discontinuation RCTs, stated durations ranged from 3 weeks to 2.2±1.3 years. In 2 Switch trials (not shown), duration ranged from "under 30 days" to 179 days. In 1 Distinguish Withdrawal from Recurrence RCT (not shown), previous treatment lasted 17 weeks. In 1 Using Withdrawal Syndrome as Therapy RCT (not shown), previous treatment lasted 1 week.

Table 5: Risk-of-discontinuation-bias assessment of 80 RCTs

	Present (1 point)		Absent (0 point)		Absent but relevance uncertain (0 point)	
	Any mention that withdrawal/ rebound symptoms may occur with disc of drug/ drug class	Any mention that withdrawal/ rebound symptoms may trigger/lead to relapse	Any mention that withdrawal/ rebound symptoms may resemble/mimic relapse or confound its assessment	Measure of withdrawal symptoms (separate from EPS)	Any description/ analysis of withdrawal symptoms in any subgroup of participants	Any analysis of possible withdrawal confound on any study outcome

Reference	Score (max 6 pts)	Blind[1]	Treatment allocation concealment and/or blinding[2]
Arnold et al. 2004	1	DB	Inadequate
Baandrup et al. 2016	2	DB	Adequate
Baillargeon et al. 2003	0		
Baldwin et al. 2006	4	DB	I
Ballard et al. 2004	1	DB	A
Ballard et al. 2008	0	DB	I
Belleville et al. 2007	3		
Bergh et al. 2012	1	DB	I
Brams et al. 2012	0	DB	A
Buitelaar et al. 2011	3	DB	I
Chen et al. 2010	3	DB	I
Coghill et al. 2014	2	DB	I
Cortese et al. 2008	2		
Curran et al. 2003	2	DB	A
de Kuijper et al. 2014	0		
Dell'Osso et al. 2008	1	DB	I
Devanand et al. 2011	0	DB	A
Devanand et al. 2012	1	DB	I
Emsley et al. 2014	0	DB	I
Findling et al. 2015	0	DB	A
Ganguli et al. 2008	1		
Garzon et al. 2009	0	DB	
Ghaemi et al. 2010	0		A
Goodwin et al. 2009	6	DB	I
Gorenstein et al. 2005	0		
Grant & Potenza 2005	0	DB	I
Haessler et al. 2007	3	DB	I
Hartford et al. 2007	2	DB	I
Huijbers et al. 2016	2		
Judge et al. 2002	4	DB	I
Kafantaris et al. 2004	4	DB	I
Kasper et al. 2014	3	DB	A
Kennedy et al. 2014	3		
Khan et al. 2014	3	DB	A
Koran et al. 2003	0	DB	I
Koran et al. 2005	0	DB	I
Koran et al. 2007a	0	DB	I
Koran et al. 2007b	0	DB	A
Krystal et al. 2006	2		

Kudoh et al. 2003							3	DB	I
Lee 2002et al.							0		
Lemoine et al. 2006							3	DB	A
Mavissakalian & Perel 2001							0	DB	I
Mayur et al. 2000							0		
Mercier-Guyon et al. 2004							4	DB	I
Montgomery et al. 2004							5	DB	A
Morin et al. 2004							4		I
Mueser et al. 2001							0	DB	A
Nakao et al. 2006							3		
O'Connor et al. 2008							4		
Otto et al. 2010							4		
Pae et al. 2009							1		
Petrovic et al. 2002							4	DB	I
Research Units 2005							1		
Rickels et al. 2000							3		
Ristanovic et al. 2009							1		
Roehrs et al. 2012							4		
Ruths et al. 2008							3	DB	I
Saksa et al. 2004							0	DB	I
Sandler et al. 2010							1		
Schmidt et al. 2002							1		
Sunder et al. 2004							5		
Swanson et al. 2006							3	DB	A
Takeuchi et al. 2013							0		
Tandon et al. 2016							0		
Tint et al. 2008							3		
Troost et al. 2005							2		
Ulfvarson et al. 2003							1		A
Vaishnavi et al. 2006							0	DB	I
van Reekum et al. 2002							0	DB	I
Vicens et al. 2006							3		
Vicens et al. 2014							3		
Vissers et al. 2007							3		
Vöhringer et al. 2015							0		
Volavka et al. 2000							1	DB	I
Voshaar et al. 2003							4		
Weisler et al. 2009							3	DB	A
Zahir et al. 2000							2		
Zarate & Tohen 2004							0	DB	A
Zitman & Couvee 2001							3	DB	I

Notes to Table 4: 1. 45 studies reported double-blinding of discontinuation phase. 2. "Adequate" meant that treatment allocation concealment was executed by an independent party and that active drugs and placebos had identical appearance.

Minimum score: 0

Maximum score: 6

Mean ± SD: 1.81 ± 1.61

Median score: 2

Mode: 0