Best Evidence Summaries of Topics in Mental Healthcare

BEST *in* MH *clinical question-answering service*

Question

'In adults with learning disabilities how effective are pharmacological interventions in the management of challenging behaviour?'

Clarification of question using PICO structure

Patients: Adults with learning disabilities
Intervention: Any pharmacological intervention
Comparator: Treatment as usual
Outcome: Reduction in challenging behaviour.

Clinical and research implications

The studies included in this evidence summary do not provide strong support for the effectiveness of any pharmacological intervention in reducing challenging behaviour in adults with learning disabilities. There was some, very limited evidence (one very small RCT included in a systematic review) that risperidone may have some effectiveness in managing challenging behaviour in adults with autistic disorders. Evidence on the effectiveness of risperidone for the management of challenging behaviour in adults with learning disabilities was contradictory; one high quality RCT found no statistically significant difference between risperidone and placebo on any behavioural measure and one moderate quality RCT found significant improvements in Aberrant Behaviour Checklist (ABC) score, Behaviour Problems Inventory (BPI) and care giver-assessed VAS scale for aggressive behaviour associated with risperidone treatment compared to placebo. There was no evidence for a significant treatment effect associated with any other antipsychotic medication assessed. One systematic review, which had a number of methodological limitations, provided some evidence to support the use of lithium and some antiepileptic mood stabilizer medications for the management of behaviour problems in adults with learning disabilities; the authors of this review noted the methodological weakness of included studies and advised cautious interpretation.

Further research is needed to determine the effectiveness of pharmacological interventions in managing challenging behaviour in adults with learning disabilities. In particular, further RCTs are needed to confirm the effectiveness, or otherwise, of antipsychotic medications in managing challenging behaviour in adults with autistic disorders.

What does the evidence say?

Number of included studies/reviews (number of participants)

We identified two systematic reviews[1,2] and two randomised controlled trials (RCTs), [3,4] which met the inclusion criteria for this evidence summary. One systematic review aimed to assess the effectiveness of antipsychotic medication for people with learning disability and challenging behaviour without additional mental illness.[1] This systematic review included nine RCTs, however, only two of these (one conducted in adults with severe learning disabilities and one in adults with autistic disorder) reported data for behavioural outcome measures; these studies compared eltoprazine with placebo and risperidone with placebo, respectively.[1] The second systematic review aimed to assess the effectiveness of mood stabilizers in the management of behaviour problems among adults with intellectual disability.[2] This review included seven studies, of various designs, which assessed lithium, valporate, topiramate and carbamazepine.[2] The two RCTs both compared antipsychotic medication (risperidone,[3] and risperidone or haloperidol[4]) with placebo, for the management of challenging behaviour in adults with intellectual disability.

Main Findings

One systematic review included an RCT (n = 160), which found no significant difference between eltoprazine and placebo in behavioural measures in adults with learning disabilities and challenging behaviour, measured after eight weeks of treatment.[1] The same systematic review included a second small RCT (n = 31), which reported differences in Clinical Global Impression (CGI) (OR 0.06 (95% CI: 0.01 to 0.38) and Ritvo-Freeman Real-life Rating Scale (mean difference -0.13 (95% CI: -0.38 to 0.12), which favoured risperidone over placebo.[1] A second systematic review, which included seven, mostly un-controlled observational studies, provided some limited evidence for improvements in behavioural measures in patients treated with lithium, valporate, or topiramate; one comparative study showed no difference between carbamazepine and placebo.[2] Two additional RCTs, not included in the systematic reviews, assessed the effectiveness of antipsychotic medications for the management of challenging behaviours in adults with intellectual disabilities.[3,4] The first RCT (n = 77) reported significant improvements, after four weeks of treatment with risperidone compared to placebo, in Aberrant Behaviour Checklist (ABC) scores (-27.3 ± 3.3 versus -14.9 ± 4.0), Behaviour Problems Inventory (BPI) (−0.8 ± 0.4 versus placebo −0.2±0.3) and care giver-assessed VAS scale for aggressive behaviour (decrease of 31.3, versus 12.8); improvements in ABC and VAS were continued through a 48 week open label phase.[3] The second RCT (n=86) reported no statistically significant differences, in any behavioural measure (including Modified Overt Aggression Scale (MOAS), ABC and CGI) at 4, 12, or 26 weeks, between patients treated with risperidone or haloperidol and those receiving placebo.[4]

Authors Conclusions

One systematic review and one additional RCT concluded that there was insufficient evidence to support the effectiveness of antipsychotic medication for the management of challenging behaviour in adults with learning disability.[1,4] The systematic review stated that there is an urgent need for randomised controlled trials of the efficacy of antipsychotic medication in the treatment of adults with learning disability and challenging behaviour.[1] One additional RCT concluded that risperidone is efficacious and well tolerated in managing disruptive behaviour in adults with learning disabilities.[3] A second systematic review concluded that there is some evidence to support the use of lithium and some antiepileptic mood stabilizer medications for the management of behaviour problems in adults

with learning disabilities, but noted the methodological deficiencies of the primary studies identified and advised cautious interpretation.[2]

Reliability of conclusions/Strength of evidence
One, high quality Cochrane systematic review and one additional small (n = 86), high quality RCT concluded that there was insufficient evidence to support the effectiveness of antipsychotic medication for the management of challenging behaviour in adults with learning disability.[1,4] However, it should be noted that only two of the nine RCTs included in the Cochrane review reported data on behavioural outcomes and, of these, one small (n = 31) RCT suggested that risperidone may have some effectiveness in managing challenging behaviours in adults with autistic disorders. In contrast, a second small (n = 77) RCT, of moderate quality, also not included in the systematic review, reported that risperidone was associated with significant improvements in a number of behavioural measures (Aberrant Behaviour Checklist (ABC) score, Behaviour Problems Inventory (BPI) and care giver-assessed VAS scale for aggressive behaviour) compared with placebo.[3] A second systematic review, which had a number of methodological limitations, provided some evidence to support the use of lithium and some antiepileptic mood stabilizer medications for the management of behaviour problems in adults with learning disabilities.[2] However, the authors noted the methodological weakness of included studies and advised cautious interpretation.

What do guidelines say?

The only relevant guidelines identified were regarding Autism. No other diagnoses were discussed.

NICE; Autism pg. 29-30
"Consider antipsychotic medication in conjunction with a psychosocial intervention for challenging behaviour when there has been no or limited response to psychosocial or other interventions (such as environmental adaptations). Antipsychotic medication should be prescribed by a specialist and quality of life outcomes monitored carefully. Review the effects of the medication after 3–4 weeks and discontinue it if there is no indication of a clinically important response at 6 weeks. Consider antipsychotic medication for challenging behaviour on its own when psychosocial or other interventions could not be delivered because of the severity of the challenging behaviour. Antipsychotic medication should be prescribed by a specialist and quality of life outcomes monitored carefully. Review the effects of the medication after 3–4 weeks and discontinue it if there is no indication of a clinically important response at 6 weeks. Do not routinely use anticonvulsants for the management of challenging behaviour in adults with autism."

We identified some very limited evidence, from one small RCT included in a systematic review, that risperidone may have some effectiveness in the management of challenging behaviours in adults with autistic disorders. We did not identify any further evidence in support of the NICE guideline.

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Date answer completed: 22/04/2013

References

Guidelines

National Institute for Health and Care Excellence (2012) Autism: recognition, referral, diagnosis and management of adults on the autism spectrum CG142. London: National Institute for Health and Care Excellence.
http://www.nice.org.uk/nicemedia/live/13774/59685/59685.pdf

SRs

1. Bylewski, J. and Duggan, L. (2004) Antipsychotic medication for challenging behaviour in people with learning disability. *Cochrane Database of Systematic Review Issue 3*.

2. Deb,S., Chaplin, R., Sohanpal, S., Unwin, G., Soni, R. and Lenotre, L. (2008) The effectiveness of mood stabilizers and antiepileptic medication for the management of behaviour problems in adults with intellectual disability: a systematic review. *Journal of Intellectual Disability Research 52* (2) pp. 107-113.

RCTs

3. Gagiano, C., Read, S., Thorpe, L., Eerekens, M. and Van Hove, I. (2005) Short and long-term efficacy and safety of resperidone in adults with disruptive behaviour disorders. *Psychopharmacology 179*. pp. 629-636.

4. Tyrer, P., Oliver-Africano, P., Romeo, R., Knapp, M., Dickens, S., Bouras, N., Ahmed, Z., Cooray, S., Deb, S., Murphy, D., Hare, M., Meade, M., Reece, B., Kramo, K., Bhaumik, S., Harley, D., Regan, A., Thomas, D., Rao, B., Karatela, S., Lenôtre, L., Watson, J., Soni, A., Crawford, M., Eliahoo, J. and North, B. (2009) Neuroleptics in the treatment of aggressive challenging behaviour for people with intellectual disabilities: a randomised controlled trial (NACHBID) *Health Technology Assessment 13* (21).

Results

Systematic Reviews

Author (year)	Search Date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Brylewski and Duggan (2004)	12/2003	*Patients:* Studies of adults over 18 years with both learning disability (however diagnosed) and challenging behaviour (however diagnosed) without a superimposed mental illness. *Intervention:* Any antipsychotic medication, regardless of dosage, of longer than one month's duration. *Comparator:* Placebo *Outcome:* Primary outcomes were Challenging behaviours, general social functioning, adverse events, and acceptability of care (measured by drop out rates). Secondary outcomes were satisfaction of client or primary carer, non-specific general improvement in behaviour, economic outcomes, physical morbidity and mortality, and outcomes related to place of learning.	9 (n = 419, range 18 to 160)	This review aimed to determine the effectiveness of antipsychotic medication for people with learning disability and challenging behaviour without additional mental illness. Study participants had moderate to severe learning difficulties and were in-patients, with the exception of one study which was conducted in adults with autistic disorder of whom a minority were of normal intelligence. Where reported the mean age of study participants ranged from 23 to 48 years and between zero and 71% were male. The interventions assessed by included studies were SCH-12679, eltoprazine, milenperone, thioridazine, pipothiazine palmitate, prothipendyl, penfluridol, pipamperone and risperidone. The duration of included studies ranged from 3 weeks to six months. Data on behavioural outcomes were limited. One study (n =160) reported no significant difference in global impression of behaviour between eltoprazine and placebo at 8 weeks. This study also reported no	A clear objective was stated and appropriate inclusion criteria, to address this objective, were defined. Literature searches included five bibliographic databases and additional sources. The review process (study selection, data extraction and assessment of the methodological quality of included studies) included measures to minimise error and

				significant differences for indirect measures of behaviour such as increased need for isolation medication or restraint, increased need for attention, less privileges obtained, less social activities. The study of adults with autistic disorder (n = 31) reported differences in clinical global impression (OR 0.06 (95% CI: 0.01 to 0.38), n = 24) and Ritvo-Freeman Real-life Rating Scale (mean difference -0.13 (95% CI: -0.38 to 0.12), n = 30), which favoured risperidone over placebo.	bias. The methodological quality of included studies was assessed using methods described in the Cochrane Handbook. The narrative summary used for behavioural outcomes was appropriate.
Deb et al. (2008)	06/2006	*Patients:* Studies of adults (18 years of age or older) with intellectual disabilities (IQ below 70 or as defined by individual study authors) who displayed behaviour problems (as defined by individual study authors) were included in this review. Studies in which participants presented with a co-morbid psychiatric diagnosis, pervasive developmental disorder, attention deficit hyperactivity disorder, autistic spectrum or personality disorder were included if the study intervention was directed at primarily and specifically treating a behaviour problem. *Intervention:* An*y* mood stabilizers or antiepileptic medications that are mentioned in the British National Formulary 50 (BNF March 2006).	7 (n = 220, range 10 to 66)	This review aimed to assess the effectiveness of mood stabilizers in the management of behaviour problems among adults with intellectual disability. No details of participant characteristics were reported. The interventions assessed by included studies were lithium, valporate, topiramate, and carbamazepine. Duration of follow-up varied widely (between four months and ten years). Lithium (3 studies): One cross-over trial (n = 52) targeted aggression, self-injurious behaviour (SIB), destructive behaviour, tantrums and hyperactivity and found that 56% of	A clear objective was stated and appropriate inclusion criteria, to address this objective, were defined. Literature searches included four bibliographic databases. It was not clear whether the review

		Comparator: Not specified; studies without a control/comparator group were eligible for inclusion. *Outcome:* Reduction of problem behaviour.		participants improved on lithium, whilst 44% remained un-changed. One retrospective, un-controlled study (n = 66) targeted aggression, SIB and hyperactivity and found that 47% of participants improved in lithium (77% of whom required additional medication), whilst 53% remained un-changed. One RCT (n = 42) compared lithium to placebo and targeted aggression. This trial found that 73% of the lithium group improved, 9% got worse and 18% remained unchanged; 30% of the placebo group improved. Valporate (2 studies): One prospective, un-controlled study (n = 28) targeted SIB, aggression, hyperactivity, disorganized behaviour, stereotypies and impulsivity, and found that 68% of participants showed some improvement on valporate, whilst 32% remained un-changed. A second, retrospective, un-controlled study (n = 28) primarily targeted SIB and aggression and found that 71% of participants markedly improved on valporate, 21% mildly improved, 1 remained unchanged and 1 got worse. Topiramate (1 study): One retrospective, un-controlled study (n = 22) targeted aggression, SIB and destructive/disruptive behaviour and found that 74% of participants improved on topiramate, 1 remained un-changed and 4 got worse.	process (study selection, data extraction and assessment of the methodological quality of included studies) included measures to minimise error and bias. No assessment of the methodological quality of included studies was reported. A narrative synthesis was appropriate for the studies identified, however, the summary presented was weak and lacked structure.

				Carbamazepine (1 study): One cross-over study (n = 10) targeted over activity and found that 40% of participants improved on carbamazepine and 40% improved on placebo.	

RCTs/DTAs

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Gagiano et al. (2005)	*Patients:* 18–65 years and had a DSM-IV Axis I diagnosis of conduct disorder, oppositional defiant disorder, antisocial personality disorder, disruptive behaviour disorder, or intermittent explosive disorder. Also had to have a DSM-IV Axis II diagnosis of borderline intellectual functioning, or mild or moderate mental retardation, representing an intelligence quotient range of 35–84 (measured at screening using the Wechsler or Stanford–Binet IQ tests). Patients were excluded if they had a diagnosis of schizophrenia and other psychotic disorders or pervasive developmental disorder; head injury as a cause of mental impairment (except for birth trauma); seizure disorder requiring medication; clinically relevant abnormal laboratory values outside the normal range; serious or progressive illnesses (including but not limited to liver or renal insufficiency; cardiac, vascular, gastrointestinal, pulmonary, or endocrine disturbances; or human	n = 77 (39 in the risperidone group and 38 in the placebo group)	This study aimed to assess the efficacy and safety of risperidone in the treatment of disruptive behaviour disorders in intellectually disabled adults. There were no apparent significant differences in baseline demographic characteristics, IQ, diagnoses, or concomitant medication, between the risperidone and placebo groups. Study participants were aged between 18 and 59 years and had IQs of between 35 and 82; 61% were male. The mean dose of risperidone, during the double-blind phase, was 1.45±0.08 mg/day and the mean dose during the open label phase was 1.81±0.13 mg/day. The median duration of treatment was 334 days (range 16 to 400 days). All randomised participants who had taken study medication and had at least one post-baseline assessment were included in the intention-to-treat analyses. Four patients in each group discontinued the study prematurely. No patient discontinued because of adverse events. Of the patients in the double-blind study, 58 continued to the open-label study (31 had received placebo and 27 had received	Randomisation procedures and allocation concealment were not described. The initial four week phase of the trial was described as 'double blind'. This was followed by a 48 week open label phase. It was not clear whether any or all outcome assessments were conducted blind to intervention. All randomised participants who

	immunodeficiency virus infection); history of tardive dyskinesia or neuroleptic malignant syndrome; or a known hypersensitivity to antipsychotics. Patients who had previously received risperidone for conduct disorder for more than 3 weeks, or for less than 3 weeks without response, were also excluded. *Intervention:* Risperidone tablets *Comparator:* Placebo *Outcome:* The primary outcome measure was disruptive behaviour according to the Aberrant Behavior Checklist (ABC) (Aman et al. 1985). Secondary outcome measures were the Behaviour Problems Inventory (BPI), Clinical Global Impressions—Severity scale (CGI-S), and visual analog scale (VAS) for individual target behaviours.		risperidone). Twenty-six patients (44.8%) withdrew from the open-label study; the most common reasons were withdrawal of consent (13.8%) and adverse effects (10.3%). Over the four week double-blind phase, the mean change from baseline in ABC score was significantly greater in the risperidone group (-27.3 ± 3.3) than in the placebo group (-14.9 ± 4.0), p = 0.036. There were further significant improvements in ABC scores during the open label phase, both for patients initially on risperidone and those who switched to risperidone. Patients receiving risperidone showed significantly greater improvements in BPI (−0.8 ± 0.4), during the double-blind phase, than those receiving placebo (−0.2±0.3), p < 0.05; this oucome was not assessed during the open label phase. There was a trend towards greater improvement in GGI-S scores in the risperidone group compared to the placebo group, during the double blind phase, but this difference did not reach statistical significance; the severity of behavioural disturbances decreased further during the first month of the open label phase. Between week 2 and the end of the double-blind phase, patients in the risperidone group had significantly greater improvements on the care giver-assessed VAS scale for aggressive behaviour than those in the placebo group (decrease of 31.3, versus 12.8, P<0.001); improvements were maintained in the open label phase.	had taken study medication and had at least one post-baseline assessment were included in the intention-to-treat analyses. Data were reported for all listed outcome measures.
Tyrer et al. (2009)	*Patients:* Adults aged 18-65, treated by intellectual disability services in England, Wales and Queensland,	n = 86 (29 in the risperidone	This study aimed to compare the effectiveness and cost-effectiveness of haloperidol, risperidone and placebo for the management of aggressive challenging behaviour in adults with intellectual disability.	The randomisation code and its nature,

	Australia. Included patients from all severity levels of intellectual disability, extended recruitment to include those who may have been treated with neuroleptic drugs in the past, and excluded only those who had previously been diagnosed as having a psychosis. Those with autistic spectrum disorders were included provided psychosis was absent. However, those who had taken depot neuroleptics, any other form of injected neuroleptic medication within the last 3 months, or continuous oral neuroleptic medication within the last week, were excluded. Intervention: Risperidone or Haloperidol Comparator: Placebo Outcome: The primary outcome measure was the reduction in aggressive episodes between baseline and after 4 weeks of treatment, measured using the Modified Overt Aggression Scale (MOAS). Secondary outcome measures were the Aberrant Behaviour Checklist (ABC), Uplift/Burden Scale, a 40-item Quality of Life Questionnaire, Udvalg for Kliniske Undersøgelser scale, and the Clinical Global Impressions scale (CGI).	group, 28 in the haloperidol group and 29 in the placebo group)	Of the 86 included participants, 31 had mild intellectual disability, 41 had moderate disability and 14 had severe or profound intellectual disability; the distribution was similar across the three treatment groups. The mean age of study participants was 40 years; there were no apparent differences in age or gender distribution between the three treatment groups. There were no statistically significant differences in baseline behavioural measures between the three treatment groups. The mean doses of risperidone and haloperidol, during the first four weeks of the trial, were 1.15 mg and 2.73 mg, respectively. The mean doses of risperidone and haloperidol, between weeks 4 and 12, were 1.78 mg and 2.94 mg, respectively. All participants remained in the trial at the four week assessment. At 12 weeks, 21 (72%) of participants in the placebo group, 18 (62%) of participants in the risperidone group and 22 (79%) of participants in the haloperidol group remained in the trial. All three treatments were associated with reductions in MOAS aggression score of > 70% during the first week. AT four weeks the placebo group showed greater improvement than the two active treatment groups, though this difference did not reach statistical significance. No significant differences were found, between the three treatment groups, for any of the secondary outcome measures at four weeks. The 12 and 26 weeks assessments showed no significant differences between the groups, on any measure.	known only to the independent statistician from the Medical Research Council (MRC) Complex Interventions Collaborative Group used a permuted blocks technique. A part-time trial statistical assistant recorded all data and these data were not available to any other investigator. Participants and treating clinicians were blind to treatment during the study; treatments were given in the form of identical white tablets. Follow-up assessments were conducted

				independently. The main analysis of 4-week MOAS scores was conducted on an ITT basis. Data were reported for all listed outcome measures.

Risk of Bias: SRs

Author (year)	Risk of Bias				
	Inclusion criteria	Searches	Review Process	Quality assessment	Synthesis
Brylewski 2004	☺	☺	☺	☺	☺
Deb 2008	☺	☺	?	☹	☹

RCTs

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Gagiano 2005	?	?	☺	?	☺	☺
Tyrer 2009	☺	☺	☺	☺	☺	☺

☺ Low Risk ☹ High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	Learning disabilit* Intellectual disabilit* Challenging behaviour	471	1
DARE	1 ((learning OR mental OR intell* or cognitive) adj2 (handicap* OR disab* OR retard OR difficult* OR impair* OR subnormal*)) IN DARE 400 2 MeSH DESCRIPTOR Learning Disorders EXPLODE ALL TREES 15 3 MeSH DESCRIPTOR Intellectual Disability EXPLODE ALL TREES 135 4 ((challeng* OR difficult* OR antisocial) adj2 behavio*) IN DARE 49 5 (agitat*) IN DARE 124 6 (aggressi*) IN DARE 275 7 (behavio*):TI IN DARE 534 8 (behavio*) IN DARE 2713 9 #1 OR #2 OR #3 513 10 #4 OR #5 OR #6 OR #7 OR #8 2929 11 #9 AND #10 146	146	1
Primary studies			
PsycINFO	1. PsycINFO; (learning adj3 disabilit*).ti,ab; 13684 results. 2. PsycINFO; (learning adj3 disable*).ti,ab; 6902 results. 3. PsycINFO; (learning adj3 difficult*).ti,ab; 4837 results. 4. PsycINFO; (learning adj3 handicap*).ti,ab; 431 results. 5. PsycINFO; (intellect* adj3 disabilit*).ti,ab; 7530 results. 6. PsycINFO; (intellect* adj3 disable*).ti,ab; 401 results. 7. PsycINFO; (intellect* adj3 impair*).ti,ab; 1274 results. 8. PsycINFO; (cognitive* adj3 impair*).ti,ab; 22077 results. 9. PsycINFO; (mental* adj3 incapacit*).ti,ab; 189 results. 10. PsycINFO; (mental* adj3 deficien*).ti,ab; 2863 results.	123	

	11. PsycINFO; "down* syndrome".ti,ab; 5476 results. 12. PsycINFO; ((ADHD OR "attention deficit hyperactivity disorder")).ti,ab; 18044 results. 13. PsycINFO; *LEARNING DISABILITIES/; 16695 results. 14. PsycINFO; 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13; 79898 results. 15. PsycINFO; (challeng* adj2 behavio*).ti,ab; 2690 results. 16. PsycINFO; (problem* adj2 behavi*).ti,ab; 27843 results. 17. PsycINFO; (aggress* OR violen*).ti,ab; 106020 results. 18. PsycINFO; 15 OR 16 OR 17; 132191 results. 19. PsycINFO; 14 AND 18; 5243 results. 20. PsycINFO; exp DRUGS/; 226805 results. 21. PsycINFO; exp NEUROLEPTIC DRUGS/; 23641 results. 22. PsycINFO; 20 OR 21; 226805 results. 23. PsycINFO; 19 AND 22; 470 results. 26. PsycINFO; (random* OR RCT).ti,ab; 117518 results. 30. PsycINFO; CLINICAL TRIALS/; 6646 results. 31. PsycINFO; random*.ti,ab; 117217 results. 33. PsycINFO; (doubl* adj3 blind*).ti,ab; 17119 results. 34. PsycINFO; (singl* adj3 blind*).ti,ab; 1456 results. 35. PsycINFO; EXPERIMENTAL DESIGN/; 8570 results. 37. PsycINFO; (clinical adj3 study).ti,ab; 7214 results. 38. PsycINFO; trial.ti,ab; 61716 results. 39. PsycINFO; "treatment outcome clinical trial".md; 23678 results. 40. PsycINFO; 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39; 525594 results. 41. PsycINFO; 23 AND 40; 163 results. 42. PsycINFO; 30 OR 31 OR 33 OR 34 OR 35 OR 37 OR 38 OR 39; 185085 results. 43. PsycINFO; 26 OR 42; 185349 results. 44. PsycINFO; 23 AND 43; 123 results.		
Embase	18. EMBASE; (learning adj3 disabilit*).ti,ab; 7341 results. 19. EMBASE; (learning adj3 disable*).ti,ab; 1377 results. 20. EMBASE; (learning adj3 difficult*).ti,ab; 3145 results.		

	21. EMBASE; (learning adj3 handicap*).ti,ab; 109 results. 22. EMBASE; (intellect* adj3 disabilit*).ti,ab; 7545 results. 23. EMBASE; (intellect* adj3 disable*).ti,ab; 399 results. 24. EMBASE; (intellect* adj3 impair*).ti,ab; 1827 results. 25. EMBASE; (mental* adj3 incapacit*).ti,ab; 273 results. 26. EMBASE; (mental* adj3 deficien*).ti,ab; 2006 results. 27. EMBASE; "down* syndrome".ti,ab; 19152 results. 28. EMBASE; ((ADHD OR "attention deficit hyperactivity disorder")).ti,ab; 20653 results. 29. EMBASE; *LEARNING DISABILITIES/; 0 results. 30. EMBASE; (challeng* adj2 behavio*).ti,ab; 1670 results. 31. EMBASE; (problem* adj2 behavi*).ti,ab; 17502 results. 32. EMBASE; (aggress* OR violen*).ti,ab; 190776 results. 33. EMBASE; *LEARNING DISORDER/; 10413 results. 34. EMBASE; 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 33; 65806 results. 35. EMBASE; 30 OR 31 OR 32; 207438 results. 36. EMBASE; *DRUG THERAPY/; 159708 results. 37. EMBASE; exp *CENTRAL NERVOUS SYSTEM AGENTS/; 0 results. 38. EMBASE; exp *NEUROLEPTIC AGENT/; 101444 results. 39. EMBASE; dt.fs; 2895020 results. 40. EMBASE; 36 OR 38; 254798 results. 41. EMBASE; 34 AND 35 AND 40; 139 results. 42. EMBASE; 34 AND 35 AND 40; 139 results.		
Medline	34. MEDLINE; (learning adj3 disabilit*).ti,ab; 5819 results. 35. MEDLINE; (learning adj3 disable*).ti,ab; 1310 results. 36. MEDLINE; (learning adj3 difficult*).ti,ab; 2289 results. 37. MEDLINE; (learning adj3 handicap*).ti,ab; 95 results. 38. MEDLINE; (intellect* adj3 disabilit*).ti,ab; 5361 results. 39. MEDLINE; (intellect* adj3 disable*).ti,ab; 298 results. 40. MEDLINE; (intellect* adj3 impair*).ti,ab; 1471 results. 41. MEDLINE; (mental* adj3 incapacit*).ti,ab; 199 results.		

	42. MEDLINE; (mental* adj3 deficien*).ti,ab; 1927 results. 43. MEDLINE; "down* syndrome".ti,ab; 16507 results. 44. MEDLINE; ((ADHD OR "attention deficit hyperactivity disorder")).ti,ab; 15638 results. 45. MEDLINE; *LEARNING DISABILITIES/; 8610 results. 46. MEDLINE; (challeng* adj2 behavio*).ti,ab; 1235 results. 47. MEDLINE; (problem* adj2 behavi*).ti,ab; 14314 results. 48. MEDLINE; (aggress* OR violen*).ti,ab; 152436 results. 49. MEDLINE; *LEARNING DISORDER/; 8610 results. 50. MEDLINE; 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 49; 52972 results. 51. MEDLINE; 46 OR 47 OR 48; 166003 results. 52. MEDLINE; exp *CENTRAL NERVOUS SYSTEM DEPRESSANTS/; 359984 results. 53. MEDLINE; exp DRUG THERAPY/; 1021475 results. 54. MEDLINE; 52 OR 53; 1316507 results. 55. MEDLINE; 50 AND 51 AND 54; 163 results.		
Summary	**NA**	**NA**	

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