

Best Evidence Summaries of Topics in Mental Healthcare

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

Question

“For adults with Autism, what are the most effective pharmacological interventions for reducing repetitive behaviours?”

Clarification of question using *PICO* structure

Patients: Adults with Autism
Intervention: Pharmacological interventions
Comparator: Other pharmacological interventions
Outcome: Reduction of repetitive behaviours

Plain Language Summary

A small amount of research evidence found that medication can help in reducing repetitive behaviours in adults with autism. However more research is needed to find out how effective medication is for the problem of repetitive behaviours.

Clinical and research implications

There is a lack of reliable evidence about the effectiveness of pharmacological interventions for reducing repetitive behaviours in adults with Autism. Two small RCTs (30 and 37 participants) compared fluoxetine or fluvoxamine with placebo and both found that 12 weeks of pharmacological treatment significantly reduced repetitive behaviours compared with placebo. However both were of moderate quality and neither had another pharmacological treatment as the comparator. Further research is needed, with larger sample sizes and longer follow-up periods which compares different pharmacological agents with each other, and not just to placebo.

What does the evidence say?

Number of included studies/reviews (number of participants)

We identified 2 randomised controlled trials (RCTs) that evaluated repetitive behaviours in adults with autism (n = 67) both were conducted in the USA. One RCT (n = 37) compared 12 weeks of fluoxetine with placebo in adults with an Autism Spectrum Disorder (Hollander et al. 2014). The other RCT (n = 30) compared 12 weeks of fluvoxamine with placebo in adults with a diagnosis of autistic disorder (McDougle et al. 1996). Both trials measured repetitive behaviours with the Yale-Brown Obsessive Compulsive Scale.

Main findings

One trial found that 12 weeks of fluoxetine treatment significantly reduced repetitive behaviours more than the placebo group (mean difference of 3.7 points, $p = 0.005$). More fluoxetine participants also had an improvement in obsessive compulsive behaviours for global improvement (35% vs. 0%, $p = 0.03$) and symptoms (50% vs. 8%, $p = 0.03$). In the second trial, 12 weeks of fluvoxamine treatment led to a significant reduction in repetitive thoughts and behaviour with a 36% reduction in the Yale-Brown Obsessive Compulsive Scale score compared to a 2% increase with placebo ($p < 0.003$). Significant differences were also seen between the treatments in global improvement ($p < 0.001$), maladaptive behaviour ($p < 0.001$) aggression ($p < 0.03$) and autism behavioural symptoms ($p < 0.04$).

Authors' conclusions

Hollander et al. (2014) concluded that, compared to placebo, fluoxetine treatment resulted in significantly greater improvement in repetitive behaviours and also appeared to be well-tolerated.

McDougle et al. (1996) concluded that fluvoxamine is more effective than placebo in the short term treatment of the symptoms of autistic disorder in adults.

Reliability of conclusions/Strength of evidence

Both trials were considered to be at a moderate risk of bias, and both were very small (< 40 participants). Neither reported the methods of randomisation and allocation concealment. Their main strengths were that both were double-blind, using an identical placebo capsule so that the participants and treatment providers were not aware of which treatment was being taken, and both used blinded assessment of the outcomes. Neither trial fully reported on all the outcome measures,

with one missing the results for depression and the other not clearly reporting numerical estimates for all the analyses (only graphs were provided). This evidence is not likely to be very reliable.

What do guidelines say?

Neither National Institute for Health and Care Excellence (NICE) nor Searching of Scottish Intercollegiate Guidelines Network (SIGN) guidelines comment on the most effective pharmacological interventions for reducing repetitive behaviours in adults with Autism.

Date question received: 15/04/2015

Date searches conducted: 20/05/2015

Date answer completed: 26/06/2016

References

Randomised controlled trials

Hollander, E., Soorya, L., Chaplin, W., Anagnostou, E., Taylor, B. P., Ferretti, C. J., ... & Settapani, C. (2014). A double-blind placebo-controlled trial of fluoxetine for repetitive behaviors and global severity in adult autism spectrum disorders.

McDougle, C. J., Naylor, S. T., Cohen, D. J., Volkmar, F. R., Heninger, G. R., & Price, L. H. (1996). A double-blind, placebo-controlled study of fluvoxamine in adults with autistic disorder. *Archives of General Psychiatry*, 53(11), 1001-1008.

Results

Randomised controlled trials

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Hollander et al. (2014) USA	<p><i>Participants:</i> Adults aged 18-60 meeting DSM-IV criteria for Autism Spectrum Disorder (ASD), with global severity ratings in the moderate or greater range (CGI score ≥ 4) and medication-free.</p> <p><i>Intervention:</i> Fluoxetine for 12 weeks (starting from 10 mg/day in week 1, to 20 mg/day in week 2, then increased by 20 mg/day each week to maximum of 80 mg/day)</p> <p><i>Comparator:</i> Placebo for 12 weeks</p>	37 (fluoxetine n=22, placebo n=15)	<p>This study aimed to assess the efficacy of 12-week treatment of fluoxetine compared with placebo for repetitive behaviours and global severity in adults with autism spectrum disorder.</p> <p>The participants were mostly male (69%), white (73%) with a mean age of 34.3 years and a mean IQ of 103.25. Most had a diagnosis of Asperger's syndrome (65%), 32% had autism and 3% had an unspecified pervasive developmental disorder. The mean CGI severity rating at baseline was 4.39 (SD 0.56) and the mean Yale-Brown Obsessive Compulsive Scale score was 12.27 (SD 2.45).</p>	<p>Moderate</p> <p>No details were reported about the methods of randomisation and allocation concealment.</p> <p>Study medications were dispensed in an identical double-blind fashion with a fixed schedule to ensure blinding of participants and personnel.</p> <p>Outcomes were assessed by blinded raters.</p> <p>Three participants (8%) were excluded from the analysis but for reasons unrelated to treatment.</p> <p>Not all outcome measures were fully reported as there were no results for depression.</p>

	<p><i>Outcome:</i> Primary outcome: Repetitive behaviours, measured by the Yale-Brown Obsessive Compulsive Scale. Secondary outcomes: (i) Improvement in obsessive-compulsive symptoms and overall severity, measured by the Clinical global impression (CGI) scale; (ii) Irritability, measured by the Aberrant Behaviour Checklist; (iii) Depressive symptoms, measured by the Hamilton Depression Rating Scale (HAM-D); (iv) Patient safety; (v) Compliance to medication, measured through serum blood levels.</p>		<p>Fluoxetine had a significantly greater reduction in repetitive behaviours after 12 weeks compared with placebo (mean difference 3.7, $p = 0.005$). Significantly more fluoxetine participants had an improvement in obsessive-compulsive behaviour compared with placebo with a risk ratio of 1.5 for global improvement (35% vs. 0%, $p = 0.03$) and 1.8 for symptoms (50% vs. 8%, $p = 0.03$).</p>	
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<p>McDougle et al. (1996) USA</p>	<p><i>Participants:</i> Adults with a diagnosis of autistic disorder (DSM-III-R and ICD 10). Those with schizophrenia, psychotic symptoms or illicit drug use in the past six months were excluded.</p> <p><i>Intervention:</i> Fluvoxamine (starting at 50 mg/day, increased by 50 mg every 3 or 4 days to a maximum of 300 mg/day) for 12 weeks.</p> <p><i>Comparator:</i> Placebo for 12 weeks.</p> <p><i>Outcome:</i> Repetitive behaviours, measured by a modified version of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS).</p>	<p>30 (fluvoxamine n=15, placebo n=15)</p>	<p>This study compared 12 weeks treatment with fluvoxamine with placebo for reducing interfering repetitive thoughts, behaviours and aggression in adults with autistic disorder.</p> <p>The participants were mostly male (90%), with a mean age of 30.1 years and a mean IQ of 79.9. There were no significant differences between the groups at baseline in age, sex, Autism Behavior Checklist scores or IQ.</p> <p>Fluvoxamine had a significantly greater reduction in repetitive thoughts and behaviours after 12 weeks ($p < 0.003$) compared with placebo, which was apparent after 8 weeks of treatment. After 12 weeks the Y-BOS scores decreased by 36% (from 21.4 to 13.9) with fluvoxamine but increased by</p>	<p>Moderate</p> <p>No details were reported about the methods of randomisation and allocation concealment.</p> <p>Placebo treatment was given as identical capsules to ensure blinding of participants and personnel.</p> <p>Patients, families and all members of the treatment teams were unaware of drug assignment, so outcome assessment was also blinded.</p> <p>All patients completed the study and were included in the analysis.</p> <p>Although all outcomes were reported they were not reported very clearly as summary statistics and effect sizes were missing.</p>
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	<p>Aggression, measured by the Brown Aggression Scale. Various autism symptoms such as sensory-motor behaviours, social relationships, measured by the Ritvo-Freeman Real-Life Rating Scale. Response based on the CGI global improvement score.</p>		<p>2% with placebo (from 21.5 to 21.9). Similar reductions with were also seen for the repetitive thought, and repetitive behaviours subscales. Fluvoxamine also significantly improved CGI global improvement ($p < 0.001$); maladaptive behaviour ($p < 0.001$); aggression ($p < 0.03$); and autism behavioural symptoms ($p < 0.04$).</p>	
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Results

Risk of bias

Randomised controlled trials

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Hollander et al. (2014)						
McDougle et al. (1996)						

 Low risk

 High risk

 Unclear risk

Search details

Source	Search Strategy	Number of hits	Relevant evidence identified
<i>Guidelines</i>			
NICE	autism repetitive behaviours	29	0
<i>Systematic Reviews</i>			
DARE	1 MeSH DESCRIPTOR Autistic Disorder EXPLODE ALL TREES IN DARE 71 Delete 2 MeSH DESCRIPTOR Asperger Syndrome EXPLODE ALL TREES IN DARE 5 Delete 3 (autism spectrum disorder) 53 Delete 4 (ASD) 62 Delete 5 (Asperger*) 15 Delete 6 (autis*) 238 Delete 7 (repetitive) 158 Delete 8 (obsessive) 128 Delete 9 (compulsive behav*) 6 Delete 10 MeSH DESCRIPTOR Drug Therapy EXPLODE ALL TREES 7756 Delete 11 MeSH DESCRIPTOR Pharmacology EXPLODE ALL TREES 144 Delete 12 MeSH DESCRIPTOR Pharmacology, Clinical EXPLODE ALL TREES 4 Delete 13 MeSH DESCRIPTOR Psychopharmacology EXPLODE ALL TREES 2 Delete 14 #1 OR #2 OR #3 OR #4 OR #5 OR #6 250 Delete 15 #7 OR #8 OR #9 280 Delete 16 MeSH DESCRIPTOR Medication Therapy Management EXPLODE ALL TREES 21 Delete 17 MeSH DESCRIPTOR Antidepressive Agents EXPLODE ALL TREES 888 Delete 18 #10 OR #11 OR #12 OR #13 OR #16 OR #17 8675 Delete 19 #14 AND #15 AND #18 1 Delete	1	0
<i>Primary Studies</i>			

MEDLINE	<ol style="list-style-type: none"> 1. Medline; exp AUTISTIC DISORDER/; 16331 results. 2. Medline; exp DEVELOPMENTAL DISABILITIES/; 15358 results. 3. Medline; (autism AND spectrum AND disorder).ti,ab; 5555 results. 4. Medline; ASD.ti,ab; 9829 results. 5. Medline; Asperger*.ti,ab; 1733 results. 6. Medline; autis*.ti,ab; 26002 results. 7. Medline; (repetitive AND behav*).ti,ab; 5065 results. 8. Medline; (obsessive AND behav*).ti,ab; 3807 results. 9. Medline; (compulsive AND behav*).ti,ab; 5321 results. 10. Medline; exp DRUG THERAPY/; 1122826 results. 11. Medline; exp PHARMACOLOGY/ OR exp PHARMACOLOGY, CLINICAL/ OR exp PSYCHOPHARMACOLOGY/; 326697 results. 12. Medline; 1 OR 2 OR 3 OR 4 OR 5 OR 6; 46833 results. 13. Medline; 7 OR 8 OR 9; 10154 results. 14. Medline; 10 OR 11; 1402055 results. 15. Medline; 12 AND 13 AND 14; 34 results 	34	1
EMBASE	<ol style="list-style-type: none"> 1. EMBASE; exp AUTISM/; 39722 results. 2. EMBASE; exp DEVELOPMENTAL DISORDER/; 28171 results. 3. EMBASE; exp ASPERGER SYNDROME/; 3393 results. 4. EMBASE; (autism AND spectrum AND disorder).ti,ab; 7489 results. 5. EMBASE; ASD.ti,ab; 14031 results. 6. EMBASE; Asperger*.ti,ab; 2341 results. 7. EMBASE; autis*.ti,ab; 33679 results. 8. EMBASE; (repetitive AND behav*).ti,ab; 6602 results. 9. EMBASE; (obsessive AND behav*).ti,ab; 5694 results. 10. EMBASE; (compulsive AND behav*).ti,ab; 7874 results. 11. EMBASE; exp DRUG THERAPY/; 1793762 results. 12. EMBASE; exp CLINICAL PHARMACOLOGY/ OR exp PHARMACOLOGY/; 3357802 results. 13. EMBASE; exp PSYCHOPHARMACOLOGY/; 22453 results. 	93	1

	<p>14. EMBASE; 1 OR 2 OR 4 OR 5 OR 6 OR 7; 75254 results.</p> <p>15. EMBASE; 8 OR 9 OR 10; 14135 results.</p> <p>16. EMBASE; exp ANTIDEPRESSANT AGENT/; 314227 results.</p> <p>17. EMBASE; 11 OR 12 OR 13 OR 16; 4567832 results.</p> <p>18. EMBASE; 14 AND 15 AND 17; 462 results.</p> <p>19. EMBASE; 18 [Limit to: (Human Age Groups Adult 18 to 64 years)]; 93 results.</p>		
PsycINFO	<p>1. PsycInfo; exp AUTISM/; 22665 results.</p> <p>2. PsycInfo; exp ASPERGERS SYNDROME/; 2394 results.</p> <p>3. PsycInfo; exp DEVELOPMENTAL DISABILITIES/; 10719 results.</p> <p>4. PsycInfo; exp ANTIDEPRESSANT DRUGS/ OR exp DRUG THERAPY/; 119798 results.</p> <p>5. PsycInfo; exp PHARMACOLOGY/ OR exp PSYCHOPHARMACOLOGY/; 100616 results.</p> <p>6. PsycInfo; repetitive.ti,ab; 11947 results.</p> <p>7. PsycInfo; (obsessive AND behav*).ti,ab; 5679 results.</p> <p>8. PsycInfo; (compulsive AND behav*).ti,ab; 7770 results.</p> <p>9. PsycInfo; (autism AND spectrum AND disorder).ti,ab; 6622 results.</p> <p>10. PsycInfo; ASD.ti,ab; 8070 results.</p> <p>11. PsycInfo; Asperger*.ti,ab; 3084 results.</p> <p>12. PsycInfo; autis*.ti,ab; 33618 results.</p> <p>13. PsycInfo; 1 OR 2 OR 3 OR 9 OR 10 OR 11; 38688 results.</p> <p>14. PsycInfo; 4 OR 5; 208946 results.</p> <p>15. PsycInfo; 6 OR 7 OR 8; 19616 results.</p> <p>16. PsycInfo; 13 AND 14 AND 15; 162 results.</p>	162	0
CENTRAL	<p>#1 MeSH descriptor: [Autistic Disorder] explode all trees 540</p> <p>#2 MeSH descriptor: [Asperger Syndrome] explode all trees 41</p> <p>#3 autism spectrum disorderautism spectrum disorder 418</p> <p>#4 ASDASD 422</p> <p>#5 Asperger* 127</p> <p>#6 Repetitive 2930</p> <p>#7 obsessive 1844</p>	7	0

	<p>#8 compulsive behav*compulsive behav* 950</p> <p>#9 compulsive adj6 behav*compulsive adj6 behav* 6</p> <p>#10 MeSH descriptor: [Drug Therapy] explode all trees 118769</p> <p>#11 MeSH descriptor: [Pharmacology] explode all trees 1685</p> <p>#12 MeSH descriptor: [Pharmacology, Clinical] explode all trees 24</p> <p>#13 MeSH descriptor: [Psychopharmacology] explode all trees 82</p> <p>#14 #1 or #2 or #3 or #4 or #51052</p> <p>#15 #6 or #7 or #8 or #94787</p> <p>#16 #10 or #11 or #12 or #13 119760</p> <p>#17 #14 and #15 and #16 7</p>		
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