BEST in Mental Health
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Best Evidence Summaries of Topics in Mental Healthcare

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

Question

In adults with treatment resistant psychosis, in medium/low secure services, what interventions are effective in improving patient outcomes?

Clarification of question using *PICO* structure

Patients: Adults with treatment resistant psychosis
Intervention: Any intervention
Comparator: Any/no other intervention
Outcome: Improving patient outcomes

Plain language summary

There is limited high quality research available on interventions for treatment resistant psychosis in medium/low secure services. More research is needed to adequately assess effective treatments in this area.

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Clinical and research implications

This evidence summary is based on information from two small, poor quality studies, neither of which used a conventional randomised controlled design. Both studies were conducted in long-term male hospital in-patients with schizophrenia. The available evidence indicates that switching from clozapine (or equivalent) to risperidone, or augmentation of neuroleptic medication with lithium carbonate, has no significant effect on symptoms or behaviour. Although Scottish Intercollegiate Guidelines Network (SIGN) guidance recommends consideration of a trial of clozapine augmentation with a second SGA (Second Generation Antipsychotic) for treatment resistant patients, the systematic review on which this recommendation was based found no significant overall treatment effect and only very small treatment effects, which are unlikely to be clinically significant, in the individual included studies.

All of the available evidence in this area is derived from small, poor quality studies. Although there is little or no evidence to support any treatment in addition to or in place of clozapine/'traditional neuroleptics', larger, long-term trials of adjunctive treatments may provide greater certainty.

What does the evidence say?

Number of included studies/reviews (number of participants)

We identified only two very small studies (n=20 and n=44), conducted between 19 and 25 years ago, which were considered to be potentially relevant to this evidence summary.[1,2] Neither study used a conventional randomised, controlled design; one was an observational study, using retrospectively acquired control data,[1] and the other used a "randomised consent" design (described below).[2] Both studies were conducted in long-term male in-patients with schizophrenia who exhibited violent or aggressive behaviour; one study was conducted in patients who were detained in a maximum security hospital.[2] One study assessed the effectiveness of replacing 'traditional neuroleptics' with risperidone,[1] and the other assessed the effectiveness of lithium carbonate as an adjunctive treatment to neuroleptics.[2] Studies assessed changes in symptom scores (Scale for the Assessment of Negative Symptoms (SANS)),[2] clinical functioning (Time-Sample Behavioral Checklist (TSBC)),[1] and frequency of aggressive behaviours.[1]

Main findings

The observational study, which assessed the effects of switching from 'traditional neuroleptic' medication (not specified) to risperidone, found no difference in functioning (TSBC score) between the two groups over six months; interpersonal interactions and bizarre motor sub-scores improved in both groups, but no other sub-score results were reported and there was no change in the frequency of aggressive behaviour in either group.[1] Similarly, the second study found that adding lithium carbonate to neuroleptic medication in clinically optimal doses had no significant effect on symptoms in the short term (4 weeks).[2]

Authors conclusions

Beck 1997 – For forensic patients with chronic schizophrenia, risperidone failed to produce therapeutic effects, in overall clinical functioning and aggressive behaviours, that were significantly different from traditional neuroleptics.

Collins 1991 - The addition of lithium carbonate to the treatment regimen did not result in symptomatic improvement in patients completing the treatment protocol.

Reliability of conclusions/Strength of evidence

The available evidence was very sparse (two very small studies) and of poor methodological quality (neither study used conventional randomised, controlled design). Assessment using the Cochrane risk of bias tool was not considered appropriate, as this tool is designed for use with randomised controlled trials. A summary of the methodological weakness of both studies is provided in the 'risk of bias' column of the results table; overall, both studies were considered to be at high risk of bias.

What do guidelines say?

The Scottish Intercollegiate Guidelines Network (SIGN) recommends that a trial of clozapine augmentation with a second SGA (Second Generation Antipsychotic) should be considered for service users whose symptoms have not responded adequately to clozapine alone, despite dose optimisation. Treatment should be continued for a minimum of ten weeks.

Clozapine augmentation with another antipsychotic: A systematic review identified six small RCTs (n=252) of clozapine augmentation. Trials were mainly short term with the longest being 12 weeks. Response was defined as a greater than 20% improvement in PANSS or BPRS scores. Augmentation of clozapine with an antipsychotic (aripiprazole, risperidone or sulpiride) improved symptoms particularly in those receiving treatment for longer than ten weeks. A meta-analysis of double blinded randomised controlled trials of clozapine augmentation identified 10 studies examining augmentation with antipsychotics. In a small study (n=28) of sulpiride augmentation there was a significant effect with respect to BPRS/PANNS (SMD 0.83, 95% CI 0.07 to 1.59). Meta-analysis of augmentation with other antipsychotics resulted in no statistically significant effects. These findings are in agreement with previous reviews, many of which encompassed less rigorous open label studies"

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Date searches conducted: 14/09/2016
Date answer completed: 23/09/2016

References

Randomised controlled trials

1. Beck, NC., Greenfield, SR., Gotham, G., Menditto, AA., Stuve, P., Hemme, CA. (1997) Risperidone in the Management of Violent, Treatment-Resistant Schizophrenics Hospitalised in a Maximum Security Forensic Facility. *The Journal of the American Academy or Psychiatry and the Law* 25(4): pp461-468.

2. Collins, PJ., Larkin, EP., Shubsachs, APW. (1991) Lithium Carbonate in Chronic Schizophrenia – A Brief Trial of Lithium Carbonate added to Neuroleptics for Treatment of Resistant Schizophrenic Patients. *Acta Psychiatrica Scandinavica*84(2): pp150-154.

Guidelines

Scottish Intercollegiate Guidelines Network (2013). *Management of Schizophrenia.* A national Clinical Guideline (SIGN 131). http://www.sign.ac.uk/pdf/sign131.pdf

Results

Randomised controlled trials

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Beck et al (1997)	***Participants*****:** Adult males with chronic schizophrenia or schizoaffective disorder (DSM IV) hospitalised on three forensic treatment wards at a state mental hospital. All patients were enrolled in a psychosocial rehabilitation program. ***Intervention*****:** Replacement (at various time points) of neuroleptic treatment regimens with risperidone (minimum 6mg per day) ***Comparator*****:** Continuation on a neuroleptic treatment regimen ***Outcome*****:** Measures of clinical functioning and aggressive behaviours (six subscales of the Time-Sample Behavioral Checklist (TSBC), frequency of assaults or threatened assaults on other patients or staff or serious property destruction). Outcomes were examined at four time points.	n = 20 (intervention =10, control=10)	This study aimed to compare the effectiveness of risperidone to that of 'traditional neuroleptic medications' in in-patients with chronic schizophrenia. The average age of study participants was 40 years and all were male and had a history of long-term hospitalisations; the average length of continuous hospitalisation was approximately ten years. The study authors stated that 'a number of subjects had high rates of aggressive behaviour,' but did not specify the number of participants or frequency of incidents. All participants were on neuroleptics at the start of the study, but treatment regimens were not fully described; the authors stated that 'the average patient was on 2,000 mg of chlorpromazine.' Over the course of the study, the ten patients in the intervention group were taken off 'traditional neuroleptic regimens' and titrated to a minimum of 6 mg risperidone per day; no details of the	Overall, the very small sample size, non-transparent participant selection and treatment allocation processes. The open nature of the study design, retrospective assembly of control group data and insufficient participants to support the analysis methods used mean that it should be considered as having high risk of bias.

			procedure for withdrawal of 'traditional neuroleptic ', titration of risperidone or final dose of risperidone, were reported. Intervention and control groups were matched on their level of clinical functioning (TSBC scores) at baseline; no further information was provided about participant selection procedures. In the intervention group, one week summary TSBC scores were taken six months prior to the start of risperidone, three months prior to the start of risperidone, and at 3 and 6 months after achievement of 6 mg per day risperidone. Comparative TSBC measures for the control group were selected from weekly observations in matching timeframes. Clinical function data were analysed with a MANCOVA, comprising 2 groups, by 4 time intervals, by 6 TSBC sub-scores. Data on aggressive behaviour were compiled for the 6 months before and 6 months after introduction of risperidone and comparisons were made using Wilcoxon rank sum and signed rank tests. For clinical functioning (TSBC score) the main group effect and group-time interaction were not statistically significant. In both groups, the	

			interpersonal interaction and bizarre motor sub-scores improved significantly over time. No data were reported for other sub-scores. Aggression levels did not change significantly, over the course of the study, in either the risperidone or control groups.	
Collins et al 1991	***Participants*****:** In-patients who were detained in a maximum security hospital. Participants were aged 18-65 years and had a clinical diagnosis of schizophrenia (DSM-III-R), persistence of psychotic symptoms for a minimum of 6 months prior to study despite adequate neuroleptic treatment, and absence of organic brain disease. ***Intervention*****:** Addition of lithium carbonate (starting dose, 400mg twice daily, adjusted to maintain a level between 0.4 and 1.0 mmol/L) to neuroleptic medication in clinically optimal doses for those patients in the group who consented (16/21) or continuation of neuroleptic medication for those patients who refused consent (5/21) ***Comparator*****:** neuroleptic medication in clinically optimal doses ***Outcome*****:** Patients psychiatric condition using Manchester Scale modified to separate	n = 44 (intervention =21, control=23)	The study aimed to assess the effectiveness of lithium carbonate as an adjunctive treatment for resistant schizophrenia. All study participants were male and their mean age was approximately 39 years (range 21 to 65 years). The mean duration of current hospital stay was approximately 7 years (range 1 to 19 years), and the mean daily dose of chlorpromazine or equivalent, over the month prior to the study, was 1585±871 mg in the intervention group and 1154±796 mg in the control group. There were no significant differences, between the intervention and control groups, in age, sex, severity of symptoms at baseline, length of hospitalisation or concurrent neuroleptic dosage. One patient in the control group refused the initial interview and was excluded from the analyses. In the treatment group, 5 patients refused lithium, 3	Ethics committee approval for a randomised, double-blind, placebo-controlled study designed, because participants to be included were considered unlikely to able to give true consent. The study used a "randomised consent" design: Eligible participants were randomised to a "seek consent" (intervention) or

	flattening and incongruity of affect, and the Scale for the Assessment of Negative Symptoms (SANS). Outcomes were measured at baseline, week 0 and week 4.		withdrew (polydipsia), 1 was transferred and 2 did not reach adequate lithium levels; the remaining 10 completed the study protocol. For participants in the intervention group, who completed treatment, the mean lithium level (taken over weeks 2 and 3) was 0.7 mmol/L (range 0.5 to 1.3 mmol/L). There were no significant differences in symptom scores, between the treatment and control groups, at any of the assessment points. Symptom scores, in those participants in the intervention group who completed treatment, did not change significantly following lithium treatment. The mean daily chlorpromazine equivalents did not differ significantly, between the groups, at any point in the study. Comparisons between completers and non-completers found no significant differences in symptoms between the drop-out treatment group and the completed treatment group, between the drop-out treatment and control groups, or between the completed treatment and control groups.	"do not seek consent" (control) group; the intervention group were asked to consent to the addition of lithium carbonate to their normal treatment regimen and could accept or decline this addition; all patients in the intervention group (whether or not they accepted and received lithium carbonate) were compared with the control group. Overall, this study is at high risk of bias because the sample size was very small and study completion rates were very low

				in the intervention arm (25% of patients refused lithium and fewer than 50% completed the study protocol. The authors stated that the study was ‘single-blind’, but provided no further details.

Search details

Source	Search Strategy	Number of hits	Relevant evidence identified
Guidelines			
NICE	Treatment resistant Psychosis		
MEDLINE	73. Medline; ((treatment* adj2 resistant) OR (treatment-resistant)).ti,ab; 17671 results. 74. Medline; ((((treatment* adj2 resistant) OR (treatment-resistant)) adj2 (psycho* OR schizophren*))).ti,ab; 943 results. 75. Medline; exp SCHIZOPHRENIA/; 92325 results. 76. Medline; ((low OR medium) adj2 (secur*)).ti,ab; 620 results. 77. Medline; ((secur* adj2 service*)).ti,ab; 721 results. 78. Medline; ((low OR medium) adj2 (secur*) adj2 (mental adj2 health) adj2 (service* OR unit* OR setting* OR prison*)).ti,ab; 8 results. 79. Medline; ((low OR medium) adj2 (secur*) adj2 (service* OR unit* OR setting* OR prison*)).ti,ab; 230 results. 80. Medline; ((secur* adj2 psychiatric adj2 care)).ti,ab; 25 results. 81. Medline; ((forensic* adj2 (mental adj2 health) adj2 (service* OR unit* OR setting*))).ti,ab; 146 results. 82. Medline; ((forensic adj2 (service* OR setting* OR unit*))).ti,ab; 1361 results. 85. Medline; exp PRISONS/; 8601 results. 86. Medline; (((correctional* OR mental* OR psychiatric OR forensic*) adj3 institution*)).ti,ab; 2649 results. 88. Medline; exp PSYCHOTIC DISORDERS/; 45350 results. 89. Medline; exp FORENSIC PSYCHIATRY/; 60733 results. 90. Medline; exp PRISONERS/; 14174 results. 91. Medline; 73 OR 74 OR 75 OR 88; 143672 results. 92. Medline; 76 OR 77 OR 78 OR 79 OR 80 OR 81 OR 82 OR 85 OR 86 OR 89 OR 90; 82736 results. 93. Medline; 91 AND 92; 2210 results. 94. Medline; 93 [Limit to: (Document type Meta-analysis or Scientific Integrity Review)]; 9 results. 95. Medline; "randomized controlled trial".ti,ab; 45515 results. 96. Medline; "controlled clinical trial".ti,ab; 10559 results. 97. Medline; randomi$ed.ti,ab; 2 results.	307	

	98. Medline; placebo.ti,ab; 175252 results. 99. Medline; "drug therapy".ti,ab; 30476 results. 100. Medline; randomly.ti,ab; 252190 results. 101. Medline; trial.ti,ab; 419314 results. 102. Medline; groups.ti,ab; 1585124 results. 103. Medline; exp RANDOMIZED CONTROLLED TRIAL/; 0 results. 104. Medline; exp CLINICAL TRIAL/ OR exp CONTROLLED CLINICAL TRIAL/; 0 results. 105. Medline; 95 OR 96 OR 97 OR 98 OR 99 OR 100 OR 101 OR 102 OR 103 OR 104; 2111991 results. 106. Medline; 93 AND 105; 307 results.		
EMBASE	37. EMBASE; exp TREATMENT RESISTANT DISORDERS/; 0 results. 38. EMBASE; exp PSYCHOSIS/; 241541 results. 39. EMBASE; ((treatment* adj2 resistant) OR (treatment-resistant)).ti,ab; 14182 results. 40. EMBASE; ((((treatment* adj2 resistant) OR (treatment-resistant)) adj2 (psycho* OR schizophren*))).ti,ab; 1270 results. 41. EMBASE; exp SCHIZOPHRENIA/; 158626 results. 42. EMBASE; 37 OR 38 OR 39 OR 40 OR 41; 253598 results. 43. EMBASE; ((low OR medium) adj2 (secur*)).ti,ab; 842 results. 44. EMBASE; ((secur* adj2 service*)).ti,ab; 635 results. 45. EMBASE; ((low OR medium) adj2 (secur*) adj2 (mental adj2 health) adj2 (service* OR unit* OR setting* OR prison*)).ti,ab; 18 results. 46. EMBASE; ((low OR medium) adj2 (secur*) adj2 (service* OR unit* OR setting* OR prison*)).ti,ab; 357 results. 47. EMBASE; ((secur* adj2 psychiatric adj2 care)).ti,ab; 42 results. 48. EMBASE; ((forensic* adj2 (mental adj2 health) adj2 (service* OR unit* OR setting*))).ti,ab; 207 results. 49. EMBASE; ((forensic adj2 (service* OR setting* OR unit*))).ti,ab; 1754 results. 50. EMBASE; exp FORENSIC PSYCHIATRY/ OR exp FORENSIC PSYCHOLOGY/; 12276 results. 51. EMBASE; exp MENTALLY ILL OFFENDERS/; 0 results. 52. EMBASE; exp PRISONS/; 12943 results. 53. EMBASE; (((correctional* OR mental* OR psychiatric OR forensic*) adj3 institution*)).ti,ab; 3536 results. 54. EMBASE; exp OFFENDER/; 10166 results. 55. EMBASE; 38 OR 39 OR 40 OR 41; 253598 results. 56. EMBASE; 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54; 37959 results.	188	

	57. EMBASE; 55 AND 56; 3089 results. 58. EMBASE; 57 [Limit to: (EBM-Evidence Based Medicine Evidence Based Medicine or Meta Analysis or Systematic Review)]; 50 results. 59. EMBASE; random*.ti,ab; 1109313 results. 60. EMBASE; factorial*.ti,ab; 28013 results. 61. EMBASE; ((crossover* OR cross-over*)).ti,ab; 81600 results. 62. EMBASE; placebo*.ti,ab; 238576 results. 63. EMBASE; ((doubl* ADJ blind*)).ti,ab; 165558 results. 64. EMBASE; ((singl* ADJ blind*)).ti,ab; 17942 results. 65. EMBASE; assign*.ti,ab; 291603 results. 66. EMBASE; allocat*.ti,ab; 106240 results. 67. EMBASE; volunteer*.ti,ab; 205000 results. 68. EMBASE; exp "RANDOMIZED CONTROLLED TRIAL (TOPIC)"/ OR exp CONTROLLED CLINICAL TRIAL/; 664809 results. 69. EMBASE; 59 OR 60 OR 61 OR 62 OR 63 OR 64 OR 65 OR 66 OR 67 OR 68; 1877485 results. 70. EMBASE; 57 AND 69; 188 results.		
PsycINFO/CINAHL	1. PsycInfo; exp TREATMENT RESISTANT DISORDERS/; 4058 results. 2. PsycInfo; exp PSYCHOSIS/; 101786 results. 3. PsycInfo; ((treatment* adj2 resistant) OR (treatment-resistant)).ti,ab; 4895 results. 5. PsycInfo; ((((treatment* adj2 resistant) OR (treatment-resistant)) adj2 (psycho* OR schizophren*))).ti,ab; 921 results. 6. PsycInfo; exp SCHIZOPHRENIA/; 79811 results. 7. PsycInfo; 1 OR 2 OR 3 OR 5 OR 6; 107146 results. 8. PsycInfo; ((low OR medium) adj2 (secur*)).ti,ab; 1074 results. 9. PsycInfo; ((secur* adj2 service*)).ti,ab; 643 results. 13. PsycInfo; ((low OR medium) adj2 (secur*) adj2 (mental adj2 health) adj2 (service* OR unit* OR setting* OR prison*)).ti,ab; 30 results. 14. PsycInfo; ((low OR medium) adj2 (secur*) adj2 (service* OR unit* OR setting* OR prison*)).ti,ab; 579 results. 15. PsycInfo; ((secur* adj2 psychiatric adj2 care)).ti,ab; 65 results. 16. PsycInfo; ((forensic* adj2 (mental adj2 health) adj2 (service* OR unit* OR setting*))).ti,ab; 304 results. 17. PsycInfo; ((forensic adj2 (service* OR setting* OR unit*))).ti,ab; 2090 results. 19. PsycInfo; exp FORENSIC PSYCHIATRY/ OR exp FORENSIC PSYCHOLOGY/; 7610 results. 20. PsycInfo; exp MENTALLY ILL OFFENDERS/; 3379 results.	163	

	21. PsycInfo; exp PRISONS/; 6079 results. 22. PsycInfo; (((correctional* OR mental* OR psychiatric OR forensic*) adj3 institution*)).ti,ab; 4171 results. 23. PsycInfo; 8 OR 9 OR 13 OR 14 OR 15 OR 16 OR 17 OR 19 OR 20 OR 21 OR 22; 21817 results. 24. PsycInfo; 7 AND 23; 708 results. 25. PsycInfo; 24 [Limit to: (Methodology Meta Analysis or Systematic Review)]; 7 results. 26. PsycInfo; random*.ti,ab; 152777 results. 27. PsycInfo; groups.ti,ab; 413038 results. 28. PsycInfo; ((double adj3 blind)).ti,ab; 19422 results. 29. PsycInfo; ((single adj3 blind)).ti,ab; 1728 results. 30. PsycInfo; controlled.ti,ab; 95215 results. 31. PsycInfo; ((clinical adj3 study)).ti,ab; 12736 results. 32. PsycInfo; trial.ti,ab; 81511 results. 33. PsycInfo; "treatment outcome clinical trial".ti,ab; 0 results. 34. PsycInfo; exp EXPERIMENTAL DESIGN/; 51916 results. 35. PsycInfo; 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34; 667734 results. 36. PsycInfo; 24 AND 35; 163 results.		

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