

Serotonin

Introduction

Serotonin dysregulation may underlie the negative symptoms and high rates of comorbid depression seen in schizophrenia. Supporting this, selective serotonin reuptake inhibitors have been found to be effective in treating the negative symptoms of the disorder. Furthermore, acute tryptophan depletion, a dietary manipulation that lowers brain serotonin (5-HT) synthesis has been shown to worsen negative symptoms¹.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Due to the high volume of systematic reviews we have now limited inclusion to systematic meta-analyses. Where no systematic meta-analysis exists for a topic, systematic reviews without meta-analysis are included for that topic. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist which describes a preferred way to present a meta-analysis². Reviews reporting less than 50% of items have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text,

reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation ([GRADE](#)) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)³. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found one reviews that met our inclusion criteria¹.

- Moderate to high quality evidence suggests a medium effect of elevated prefrontal serotonin 5-HT_{1A} receptors in people with schizophrenia compared to controls.
- Moderate to low quality evidence suggests a medium to large effect of reduced prefrontal serotonin 5-HT_{2A} receptors in people with schizophrenia compared to controls.

Selvaraja S, Arnonec D, Cappaia A, Howes O

Alterations in the serotonin system in schizophrenia: A systematic review and meta-analysis of post-mortem and molecular imaging studies

Neuroscience and Biobehavioral Reviews 2014; 45: 233-245

[View review abstract online](#)

Comparison	Alterations in the serotonin system in people with schizophrenia vs. controls.
Summary of evidence	<p>Moderate to high quality evidence (medium sized samples, consistent, precise, direct) suggests a medium effect of elevated prefrontal serotonin 5-HT1A receptors in people with schizophrenia compared to controls.</p> <p>Moderate to low quality evidence (large samples, inconsistent, imprecise, direct) suggests a medium to large effect of reduced prefrontal serotonin 5-HT2A receptors in people with schizophrenia compared to controls.</p>
Serotonin receptors	
<p><i>Significant, medium effect of elevated prefrontal 5-HT1A receptors in people with schizophrenia;</i> 8 postmortem studies (N = 179), SMD 0.60, 95%CI 0.17 to 1.03, $p = 0.007$, I^2 48.2%, $p < 0.061$</p> <p>These results remained significant after controlling for the two common confounding variables; suicide as cause of death and antipsychotic medication status.</p> <p>Meta-regression showed a significant correlation between increased 5-HT1A levels and earlier year of publication (r-0.12, $p = 0.032$).</p> <p><i>Significant, medium to large effect of reduced prefrontal 5-HT2A receptors in people with schizophrenia;</i></p> <p>8 postmortem studies, (N = 331), SMD -0.73, CI -1.33 to -0.12, $p = 0.019$, I^2 82.3%, $p < 0.0001$</p> <p>Meta-regression showed a trend effect towards a correlation between increased age at time of death and reduced effect size (r-0.07, $p = 0.056$).</p>	
Consistency in results[‡]	Consistent for 5-HT1A receptors, inconsistent for 5-HT2A.
Precision in results[§]	Precise for 5-HT1A receptors, imprecise for 5-HT2A.

Serotonin

Directness of results	Direct
-------------------------------------	--------

Explanation of acronyms

CI = Confidence Interval, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), p = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), r = correlation coefficient, SMD = standardized mean difference, vs. = versus

Serotonin

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small⁴.

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect⁴.

Relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR of 1.00 means there is no difference between groups. A medium to large effect is considered if $RR > 2$ or < 0.5 and a large effect if $RR > 5$ or < 0.2 ⁵. Odds ratios (ORs) are similar to RRs, but they are based on the probability of an event occurring divided by the probability of that

Serotonin

event not occurring. ORs and RRs are similar in size when the event is rare, such as with schizophrenia. InOR stands for logarithmic OR where a InOR of 0 shows no difference between groups. Hazard ratios (HRs) measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforeseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (b) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) which is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula⁴;

$$I^2 = \left(\frac{Q - df}{Q} \right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed⁶.

|| Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C, which allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

Serotonin

References

1. Selvaraj S, Arnone D, Cappai A, Howes O. Alterations in the serotonin system in schizophrenia: A systematic review and meta-analysis of postmortem and molecular imaging studies. *Neuroscience and Biobehavioral Reviews*. 2014; **45**: 233-45.
2. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal*. 2009; **151**(4): 264-9.
3. GRADE Working Group. Grading quality of evidence and strength of recommendations. *British Medical Journal*. 2004; **328**: 1490.
4. Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions. 2008: Accessed 24/06/2011.
5. Rosenthal JA. Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research*. 1996; **21**(4): 37-59.
6. GRADEpro. [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*. 2008.