TITLE: Antipsychotics for the Management of Agitation in Adults with Personality Disorders or Cognitive Impairment: A Review of the Clinical Effectiveness and Guidelines

DATE: 04 September 2013

CONTEXT AND POLICY ISSUES

Antipsychotic drugs are used for treating a variety of psychiatric disorders and their off-label use is widespread. These drugs are commonly divided into two categories: first generation antipsychotics (FGA) or typical antipsychotics, and second generation antipsychotics (SGA) or atypical antipsychotics.[1] FGA includes drugs such as haloperidol, and thiothixene. SGA includes drugs such as aripiprazole, clozapine, olanzapine, quetiapine, and ziprasidone.

Psychiatric disorders are comprised of many different types and included among these are personality disorder and cognitive impairment. In psychiatric in-patients with diagnosis of personality disorder more than 50% have borderline personality disorder (BPD). The prevalence of BPD is estimated to be 1.5% to 4% in the general community and 20% among psychiatric in-patients.[2,3] BPD is associated with emotional dysregulation, impulsive aggression, and suicidal tendencies.[3]

It is common practice among psychiatrists to prescribe medications for treating borderline personality disorder.[2] However, these medications have not received marketing approval for this indication.[2,4] Prescribing practices are frequently based on anecdotal evidence rather than rigorous data.[5] Antipsychotics are being prescribed on an off-label basis for treating borderline personality disorder.[6]

The purpose of this report is to provide evidence on the clinical effectiveness of antipsychotics for reducing agitation in adults with personality disorders or cognitive impairment, who become aggressive and to summarize evidence-based guidelines on the use of antipsychotics for the management of agitation in these patients.

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RESEARCH QUESTIONS

1. What is the clinical effectiveness of antipsychotics for reducing agitation in adults with personality disorders?

2. What is the clinical effectiveness of antipsychotics for reducing agitation in adults with cognitive impairment?

3. What are the evidence based guidelines for the use of antipsychotics in the management of agitation in patients with personality disorders and/or cognitive impairment?

KEY FINDINGS

Limited evidence suggested that there may be some improvement with respect to aggression, anger or impulsivity in treating borderline personality disorder patients with antipsychotics. However, results need to be interpreted with caution as the studies were generally small in size and of short duration.

One guideline did not recommend antipsychotics for the medium- or long- term treatment of borderline personality disorder. One guideline mentioned that psychotropic agents may improve affective symptoms and impulsivity in borderline personality disorder but cautioned that there is no strong evidence base.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2013, Issue 7), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. The search was also limited to English language documents published between Jan 1, 2003 and Aug 7, 2013.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and selected potentially relevant articles for retrieval of full-text publications for further investigation and evaluated the full-text publications for final selection, according to the criteria listed in Table 1.

Table 1: Selection Criteria

Population	Adults with personality disorders Adults with cognitive impairment
Intervention	Antipsychotics
Comparator	Standard Therapy Placebo
Outcomes	Clinical effectiveness (e.g. reduced agitation, reduced aggression, calming), Safety, Guidelines

Study Designs	Health technology assessment (HTA), systematic review (SR) and meta-analysis (MA), randomized controlled trial (RCT), and non-randomized study Evidence-based guideline

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria in Table 1, if they were published prior to 2003, or duplicate publications of the same study and did not provide additional relevant information. Studies on hospitalized patients or patients at emergency services were excluded. Systematic reviews that were deemed to have incomplete reporting of outcomes, such as not reporting numerical values for outcomes, or were less current than other systematic reviews included in this report, were excluded.

Critical Appraisal of Individual Studies

Critical appraisal of a study was conducted based on an assessment tool appropriate for the particular study design. The AMSTAR checklist[7] was used for systematic reviews and the AGREE checklist[8] for guidelines.

For the critical appraisal, a numeric score was not calculated. Instead, the strength and limitations of the study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 369 citations. Upon screening titles and abstracts, 328 articles were excluded and 41 potentially relevant articles were selected for full-text review. One potentially relevant article was identified from the grey literature. Of these 42 articles, 36 did not satisfy the inclusion criteria and were excluded. Four systematic reviews[2,3,9,10] and two evidence-based guidelines[11,12] were relevant and selected for inclusion. No relevant health technology assessment, randomized controlled trial or non-randomized study were identified. Details of the study selection process are outlined in Appendix 1.

Summary of Study Characteristics

Characteristics of the included systematic reviews and guidelines are summarized below and details are provided in Appendix 2 and 3 respectively.

<u>Systematic review and meta-analysis</u>

Country of origin

Four systematic reviews[2,3,9,10] on adults with borderline personality disorder were included. All four systematic reviews also presented meta-analyses. Of the two systematic reviews published in 2011; one[9] was from the Netherlands and one[2] was from Italy. One systematic review[3] was a Cochrane review published in 2010 from Germany and one systematic review was published in 2009 from Canada.

Study designs

Of the four systematic reviews, three[3,9,10] included only RCTs and number of RCTs ranged from seven to 11, and one systematic review[2] included five RCTs and 15 open label studies. The number of patients in the included RCTs in the systematic reviews ranged between 24 and 451 with the majority of RCTs having patient numbers ≤60. The duration of the RCTs ranged between five and 24 weeks with the majority being ≤12 weeks. In the included open label studies in the systematic review, the number of patients ranged between seven and 41 and the duration ranged between eight and 52 weeks, with the majority being ≤12 weeks.

Interventions and comparators

The antipsychotic drugs included in the systematic reviews varied. Haloperidol, aripiprazole and olanzapine were considered in all four systematic reviews. Ziprasidone was considered in three systematic reviews,[2,3,9] thiothixene was considered in two systematic reviews,[2,3] trifluoperazine was considered in one systematic review,[10] and clozapine, quetiapine, risperidone, flupenthixol were considered in the open label studies of one systematic review.[2]

Outcomes

Information specifically on agitation was not available, however as aggressive behavior was of interest, outcomes such as anger, aggression, impulsivity were considered. Impulsive behavioural dyscontrol and affective dysregulation were reported in two systematic reviews,[2,9] anger and impulsivity were reported in one systematic review,[3] and anger/ aggression was reported in one systematic review.[10] Outcomes were measured using a variety of assessment tools. Information on adverse effect was sparse. Only one systematic review[3] provided details of adverse effects.

Guideline

Two guidelines[11,12] were included. One guideline[12] on the treatment and management of borderline personality disorder was from the National Institute of Clinical Excellence (NICE) in UK and was published in 2009. One guideline[11] on treatment of personality disorder was from the World Federation of Societies of Biological Psychiatry (WFSBP) and was published in 2007.

The grading of recommendations and levels of evidence used to develop the guidelines are summarized in Appendix 3.

Summary of Critical Appraisal

Systematic review

One systematic review[3] was of high quality and three[2,9,10] were of fair to good quality. All four systematic reviews stated the objective, inclusion and exclusion criteria, conducted a comprehensive literature search, described the study selection process, and listed the included studies. List of excluded studies was provided in one systematic review[3] and not provided in three systematic reviews.[2,9,10] Characteristics of individual studies were described in all four systematic reviews and extensive details were provided in one.[3] Article selection and data extraction were done in duplicate in three systematic reviews[2,3,10] and in one systematic review[9]

it was unclear. One systematic review[3] mentioned quality assessment of the included studies and three systematic reviews[2,9,10] did not. Publication bias was explored using Funnel plots in two systematic reviews[3,10] but it was difficult to determine the extent of publication bias. Two systematic reviews[2,9] did not mention exploration of publication bias. Three systematic reviews[2,3,9] mentioned conflict of interest and one[10] did not.

Guideline

In the two included guidelines[11,12] the scope and purpose were stated, the methods used for development of the guidelines were rigorous, and conflict of interest of the guideline development group was stated. In the NICE guideline[12] the guideline development group was composed of professionals in psychiatry, clinical psychology, nursing, and general practice; academic experts in psychiatry and psychology; and two service users and a carer. In the WFSBP guideline[11] the guideline development group comprised psychiatrists in active clinical practice and/ or in research; it was unclear if patient input was sought. Costs involved were discussed in one guideline[12] and not in one guideline.[11] Organizational barriers were not described in the guidelines.

Strengths and limitations of individual studies are provided in Appendix 4.

Summary of Findings

The overall findings are summarized below and findings from the individual systematic reviews and guidelines are provided in Appendix 5 and 6 respectively.

What is the clinical effectiveness of antipsychotics for reducing agitation in adults with personality disorders?

The included systematic reviews were on borderline personality disorder. Information specifically on agitation was not available, however as aggressive behavior was of interest, outcomes such as anger, aggression, impulsivity were considered. The various tools used to measure outcomes are described in Appendix 5.Statistically significant results are presented here and all results are available in Appendix 5. Two systematic reviews[2,9] showed there was statistically significant improvement in affective dysregulation or affective dysregulation-anger with antipsychotics compared with placebo. One systematic review[2] showed there was statistically significant improvement in impulsive behavioral dyscontrol with antipsychotics compared with placebo. One systematic review[10] showed that there was statistically significant improvement with respect to anger/ aggression with antipsychotics compared with placebo. One systematic review[3] considered each antipsychotic drug separately and showed that there was statistically significant improvement with respect to anger with haloperidol, aripiprazole and olanzapine compared to placebo and statistically significant improvement with respect to impulsivity with aripiprazole compared to placebo.

Adverse effects were sparsely reported in most cases. One systematic review[3] provided some details of adverse effects. It showed that weight gain, appetite increase, somnolence, and dry mouth were statistically significantly higher with olanzapine compared to placebo. One systematic review[2] mentioned that there was no significant difference in early discontinuation due to adverse events between patients on antipsychotics versus those on placebo.

What is the clinical effectiveness of antipsychotics for reducing agitation in adults with cognitive impairment?

No health technology assessment, systematic review and meta-analysis, RCT or non-randomized study on adults with cognitive impairment was identified.

What are the evidence based guidelines for the use of antipsychotics in the management of agitation in patients with personality disorders and/or cognitive impairment?

Specific recommendations relating to the management of agitation in patients with personality disorders and/or cognitive impairment were not available. However there were some general recommendations which may be useful. The NICE guideline[12] mentioned that antipsychotics should not be used for the treatment of borderline personality disorder for medium- or long-term. The WFSBP guideline[11] mentioned that psychotropic agents may improve affective symptoms and impulsivity in individuals with borderline personality disorder but cautioned that that there is no strong evidence base for the prescription of any drug. The authors of the WFSBP guideline mentioned that the efficacy of atypical antipsychotics was based on fair research-based evidence level (Level B).

Limitations

There was considerable overlap of studies included in the various systematics reviews. It should be noted that the total number of unique studies contributing to the results were less than what may appear to be, based on the number of studies reported for each systematic review.

Comparison between systematic reviews was difficult as the inclusion and exclusion criteria and method of analyses varied. In some pooled estimates for both FGA and SGA were presented together, in some pooled estimates for FGA and SGA were presented separately and in some pooled estimates or single estimates were presented for each drug separately. In addition symptom areas investigated in the systematic reviews varied.

For systematic reviews providing pooled estimates by considering different antipsychotic drugs in one analysis, it is possible that the effect of a particular antipsychotic drug may be diluted.

A wide variety of tools was used to measure outcomes and tools used varied among studies making comparison between studies difficult.

Most of the included studies were of small size (≤ 60 patients) and short duration (≤12 weeks). Efficacy data for some antipsychotics were from single studies, hence definite conclusions are difficult. As long term studies were not available, the impact of maintenance therapy over long periods for these symptoms is not known. Data on adverse events were sparse. Of the four included systematic reviews only one report contained extensive information on adverse events

It is not clear to what extent the exclusion criteria of the studies may have excluded patients typically seen in clinical practice and this could impact generalizability of the findings.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Limited evidence suggested that there may be some improvement with respect to aggression, anger or impulsivity in treating borderline personality disorder patients with antipsychotics. However, results need to be interpreted with caution as the studies were generally small in size (majority with ≤60 participants) and of short duration (majority ≤12 weeks). It should be noted that authors of the systematic reviews mentioned that there is need for more robust long term studies in order to come to definitive conclusions.

The NICE guideline did not recommend antipsychotics for the medium- or long- term treatment of borderline personality disorder. The WFSBP guideline mentioned that psychotropic agents may improve affective symptoms and impulsivity in borderline personality disorder but cautioned that there is no strong evidence base.

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REFERENCES

1. University of Alberta Evidence-based Practice Center. First- and second-generation antipsychotics for children and young adults [Internet]. Rockville (MD): Agency for Healthcare Research and Quality; 2012. [cited 2012 Dec 13]. (Comparative Effectiveness Review Number 39). Available from: http://www.ncbi.nlm.nih.gov/books/NBK84643/pdf/TOC.pdf

2. Vita A, De PL, Sacchetti E. Antipsychotics, antidepressants, anticonvulsants, and placebo on the symptom dimensions of borderline personality disorder: a meta-analysis of randomized controlled and open-label trials. J Clin Psychopharmacol. 2011 Oct;31(5):613-24.

3. Stoffers J, Vollm BA, Rucker G, Timmer A, Huband N, Lieb K. Pharmacological interventions for borderline personality disorder. Cochrane Database Syst Rev [Internet]. 2010 [cited 2013 Aug 12];(6):CD005653. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005653.pub2/pdf

4. Silk KR. Borderline personality disorder: treatment and prognosis. 2013 Mar 11 [cited 2013 Aug 30]. In: UpToDate [Internet]. Version 20.9. Waltham (MA): UpToDate; 1992 - . Available from: www.uptodate.com Subscription required.

5. Ripoll LH, Triebwasser J, Siever LJ. Evidence-based pharmacotherapy for personality disorders. Int J Neuropsychopharmacol. 2011 Oct;14(9):1257-88.

6. Maglione M, Ruelaz MA, Hu J, Wang Z, Shanman R. Off-label use of atypical antipsychotics: an update [Internet]. Rockville: AHRQ Comparative Effectiveness Review; 2011. [cited 2013 Aug 12]. Available from: http://www.effectivehealthcare.ahrq.gov/ehc/products/150/778/CER43_Off-LabelAntipsychotics_20110928.pdf

7. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol [Internet]. 2007 [cited 2013 Aug 8];7:10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf

8. The AGREE Collaboration. Appraisal of guidelines for research and evaluation (AGREE) instrument [Internet]. London: The AGREE Research Trust; 2001 Sep. [cited 2013 Jun 23]. Available from: http://www.agreetrust.org/?o=1085

9. Ingenhoven TJ, Duivenvoorden HJ. Differential effectiveness of antipsychotics in borderline personality disorder: meta-analyses of placebo-controlled, randomized clinical trials on symptomatic outcome domains. J Clin Psychopharmacol. 2011 Aug;31(4):489-96.

10. Mercer D, Douglass AB, Links PS. Meta-analyses of mood stabilizers, antidepressants and antipsychotics in the treatment of borderline personality disorder: effectiveness for depression and anger symptoms. J Pers Disord. 2009 Apr;23(2):156-74.

11. Herpertz SC, Zanarini M, Schulz CS, Siever L, Lieb K, Moller HJ, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of personality disorders. World J Biol Psychiatry. 2007;8(4):212-44.

12. National Collaborating Centre for Mental Health. Boarderline personality disorder: the NICE guideline on treatment and management [Internet].The British Psychological Society and The Royal College of Psychiatrists; 2009. [cited 2013 Aug 26]. (National Clinical Practice Guideline Number 78). Available from: http://www.nice.org.uk/nicemedia/live/12125/43045/43045.pdf

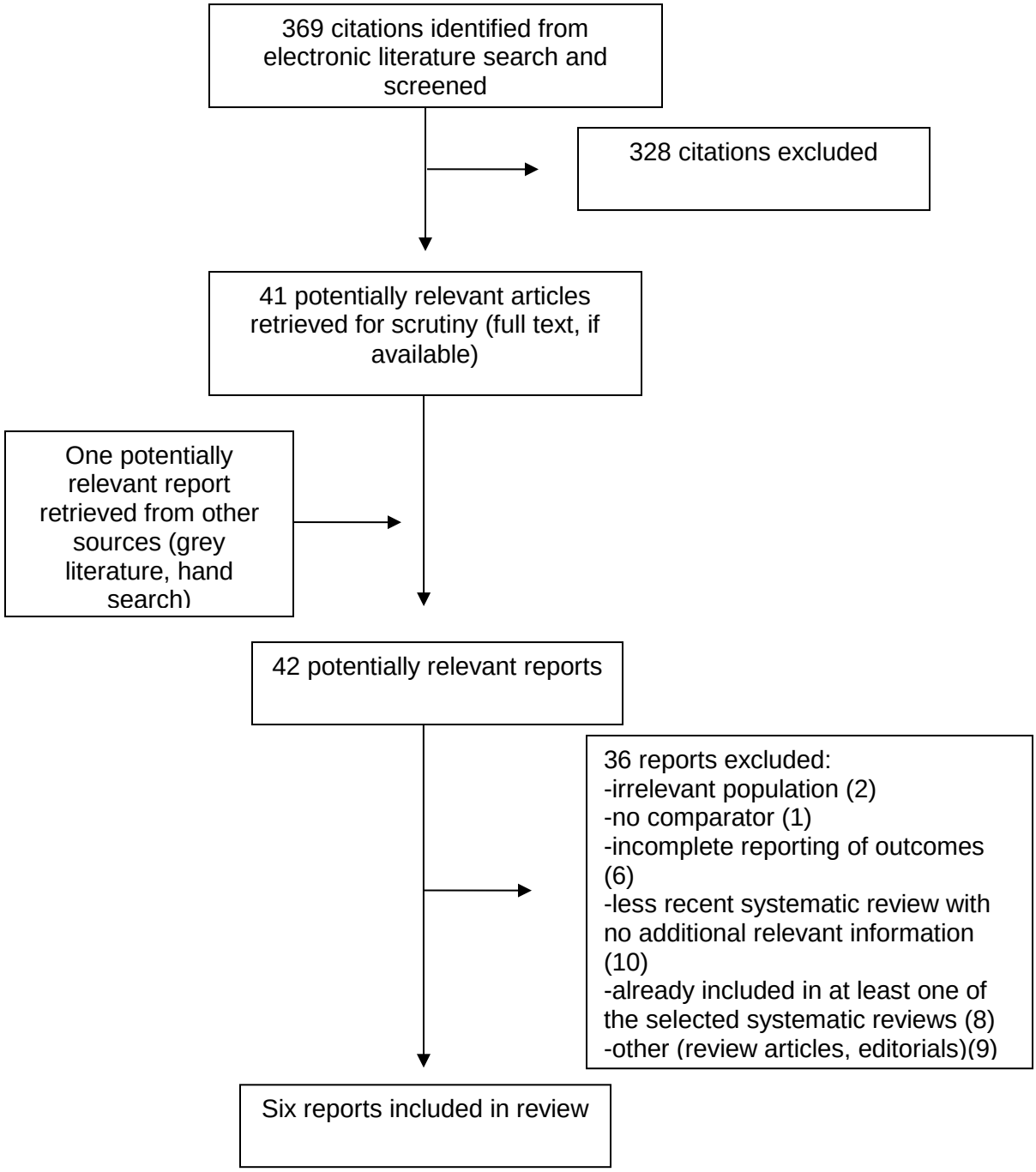
13. Vita A, De PL, Sacchetti E. Antipsychotics, antidepressants, anticonvulsants, and placebo on the symptom dimensions of borderline personality disorder: a meta-analysis of randomized controlled and open-label trials. Supplemental table A. Characteristics of studies included in the meta-analysis of RCTs. J Clin Psychopharmacol. 2011 Oct;31:613-24.

14. Vita A, De PL, Sacchetti E. Antipsychotics, antidepressants, anticonvulsants, and placebo on the symptom dimensions of borderline personality disorder: a meta-analysis of randomized controlled and open-label trials. Supplemental table B. Characteristics of studies included in the meta-analysis of open trials. J Clin Psychopharmacol. 2011 Oct;31:613-24.

ABBREVIATIONS

A	aripiprazole
AE	adverse effect
AIAQ	Anger, Irritability, and Assault Questionnaire
BDHI	Buss-Durkee Hostility Inventory
BIS	Barratt Impulsiveness Scale
BPD	Borderline Personality Disorder
BPDSI	BPD Severity Index
BPRS	Brief Psychiatric Rating Scale
C	clozapine
CGI	Clinical Global Impression
CGI-BPD	CGI scale for BPD
CI	confidence interval
F	flupenthixol
FGA	first generation antipsychotic
H	haloperidol
HSCL	Hopkins Symptoms Checklist
HSCL-HOS	HSCL-anger-hostility
MA	meta-analysis
MOAS	Modified Overt Aggression Scale
NA	not applicable
NS	not significant
O	olanzapine
OAS-M	Overt Aggression Scale Modified
Q	quetiapine
R	risperidone
RCT	randomized control trial
RR	relative risk
SCL-90	Symptom Checklist-90
SCL-90-HOS	SCL-90 hostility
SCL-90-R	Symptom Checklist-90 Revised
SD	standard deviation
SGA	second generation antipsychotic
SMD	standardized mean difference
SR	systematic review
STAXY	State-Trait Anger Expression Inventory
T	thiothixene
Tpz	trifluoperazine
WSIA	Ward Scale of Impulsive Action
Z	ziprasidone
ZAN-BPD	Zanarini Rating Scale for Borderline Personality Disorder

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Studies

First Author, Publication Year, Country	Study Design, Duration	Patient Characteristics, Sample Size (N)	Intervention	Comparators	Outcomes Measured
Systematic review and meta-analysis					
Ingenhoven,[9] 2011, Netherlands	SR/MA (9 RCTs), 5 to 21 weeks (majority ≤ 12 weeks)	Adults with BPD, N = 1284, (for individual studies patient numbers ranged from 24 to 451)	FGA (H), SGA (A,O, Z)	Placebo	Impulsive behavioral dyscontrol, Affective dysregulation-anger
Vita,[2,13,14] 2011, Italy	SR/MA (5 RCTs, 15 open-label studies), For RCTs: 5 to 12 weeks, For open label studies: 8 to 52 weeks (majority ≤ 12 weeks)	Adults with BPD, For RCTs: N = 461, (for individual studies patient numbers ranged from 35 to 314) For open label studies: N =239, (for individual studies patient numbers ranged from 7 to 41)	For RCTS: FGA (H), SGA (A, O, Z). For open label studies: FGA (F, T), SGA (A,C, O, Q, R)	Placebo	Impulsive behavioral dyscontrol, Affective dysregulation, AE
Stoffers,[3] 2010, Germany. (Cochrane review)	SR/MA (11 RCTs), 5 to 24 weeks (majority ≤ 12 weeks)	Adults with BPD, N = 752, (for individual studies patient numbers ranged from 24 to 314) (Note: Data was pooled for each antipsychotic drug separately)	FGA (H, T), SGA (A, O, Z)	Placebo	Anger, Impulsivity, AE
Mercer,[10] 2009, Canada	SR/MA (7 RCTs), 5 to 24 weeks (majority ≤ 12 weeks)	Adults with BPD, N = 319, (for individual studies patient numbers ranged from 25 to 100)	FGA (H, Tpz), SGA (A,O)	Placebo	Anger/ aggression

A = aripiprazole, AE = adverse ffect, BPD = borderline personality disorder, C = clozapine, F = flupenthixol, FGA = first generation antipsychotic, H = haloperidol, O = olanzapine, MA = meta-analysis, N = number of patients Q = quetiapine, R = risperidone, RCT = randomized controlled trial, SGA = second generation antipsychotic, SR = systematic review, Tpz = trifluoperazine, Z = ziprasidone,

Note:
In the systematic review by Vita et al.[2] two supplementary tables were referred to and were available as two separate articles[13,14]

Information presented here are for population, intervention and outcomes of interest from relevant studies that were included in the systematic review and does not include other information presented in the systematic reviews, that is not relevant for this report.

The systematic reviews included several meta-analyses and N indicates the maximum number of patients found in a meta-analysis.

APPENDIX 3: Grading of Recommendations and Levels of Evidence

Guideline Society or Institute, Year	Level of Evidence
NICE,[12] UK, 2009	The GRADE profile was used. The quality of evidence was categorized as follows. **High:** "Further research is very unlikely to change confidence in the estimate of the effect" p. 50 **Moderate:** "Further research is likely to have an important impact on confidence in the estimate of the effect and may change the estimate" p.50 **Low:** "Further research is very likely to have an important impact on confidence in the estimate of the effect and is likely to change the estimate" p.50 **Very low:** "Any estimate of effect is very uncertain" p.50
WFSBP,[11] Herpertz, Germany, 2007	**Level A:** "Good research-based evidence. This level is achieved if research-based evidence for efficacy is available from at least three moderately large (≥50 participants), positive, randomized controlled (double- blind) studies (RCT). At least one of these three studies must be a well-conducted, placebo-controlled study." P.217 **Level B:** "Fair research-based evidence. This level is achieved if research-based evidence for efficacy is available from at least two moderately large, positive, randomized, controlled (double-blind) studies (two comparator studies *or* one comparator-controlled and one placebo-controlled study) *or* from one moderately large randomized, controlled (double-blind) study (placebo-controlled or comparator controlled) and ≥1 prospective, moderately large, open-label, naturalistic study." P. 217 **Level C:** "Minimal research-based evidence to support the recommendation. This level is achieved if research-based evidence for efficacy is available from one prospective, randomized, controlled (double-blind) study (placebo-controlled or comparator-controlled) and one prospective, open-label study/ case series (with a sample size of≥10 participants) *or* at least two prospective, open-label studies/case series (≥10 participants)." P. 217 **Level D:** "Expert opinion-based (from authors and members of the WFSBPD Task Force on Personality. Disorders) supported by at least one prospective, open-label study/case series (≥10 participants)." P. 217-218 **No level of evidence:** "Expert opinion for general treatment procedures and principles." P. 218

BPD = borderline personality disorder, NICE = National Institute of Clinical Excellence, UK = United Kingdom, WFSBP = World Federation of Societies of Biological Psychiatry

APPENDIX 4: Summary of Study Strengths and Limitations

First Author, Publication Year, Country	Strengths	Limitations
Systematic review and meta-analysis		
Ingenhoven,[9] 2011, Netherlands	• The objective was clearly stated. • The inclusion and exclusion criteria were stated. • Multiple databases were searched, as well cross references from relevant articles • Study selection described • List of included studies provided • Characteristics of the individual studies were provided • Conflict of interest was stated and there appeared to be none	• List of excluded studies not provided • Unclear if article selection and data extraction were done in duplicate • No mention of quality assessment of studies • No mention of exploration of publication bias
Vita,[2] 2011, Italy	• The objective was clearly stated. • The inclusion and exclusion criteria were stated. • Multiple databases were searched, as well cross references from relevant articles • Study selection described • List of included studies provided • Article selection and data extraction were done in duplicate • Characteristics of the individual studies were provided • Conflict of interest was stated and two of the authors received grants from industry	• List of excluded studies not provided • No mention of quality assessment of studies • No mention of exploration of publication bias
Stoffers,[3] 2010, Germany. (Cochrane review)	• The objective was clearly stated. • The inclusion and exclusion criteria were stated. • Multiple databases were searched, as well cross references from relevant articles and attempts were made to obtain unpublished studies. • Study selection described • List of included and excluded studies provided • Article selection and data extraction were done in duplicate • Characteristics of the individual studies were provided • Quality assessments of studies were conducted	

First Author, Publication Year, Country	Strengths	Limitations
	• Publication bias was explored by funnel plot • Conflict of interest was stated and there appeared to be none	
Mercer,[10] 2009, Canada	• The objective was clearly stated. • The inclusion and exclusion criteria were stated. • Multiple databases were searched, as well cross references from relevant articles and attempts were made to obtain unpublished studies. • Study selection described • List of included studies provided • Article selection and data extraction were done in duplicate • Characteristics of the individual studies were provided • Publication bias was explored by funnel plot	• List of excluded studies not provided • No mention of quality assessment of studies • No mention of conflict of interest
Guidelines		
NICE,[12] UK, 2009	• The scope and purpose were clearly stated. • The guideline development group comprised of professionals in psychiatry, clinical psychology, nursing, and general practice; academic experts in psychiatry and psychology; and two service users and a carer • The methods used for the development of the guidelines were rigorous. • Costs involved were discussed. • Recommendations were clear • Conflict of interest of guideline development members were stated and some members received grants from industry	• Organizational barriers were not discussed.
WFSBP,[11] Herpertz, Germany, 2007	• The scope and purpose were clearly stated. • The guideline development group comprised of psychiatrists in active clinical practice and/ or in research • The methods used for the development of the guidelines	• Unclear if patient input was sought • Costs involved or organizational barriers were not discussed.

First Author, Publication Year, Country	Strengths	Limitations
	were rigorous. • Recommendations were clear • Conflict of interest of guideline development members were stated and it was mentioned that some may have received funds related to treatments discussed in the guidelines	

APPENDIX 5: Main Study Findings and Authors' Conclusions

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td colspan="2">Systematic review and meta-analysis</td></tr>
<tr><td>Ingenhoven,[9] 2011, Netherlands</td><td>
Main Findings:

Comparison of antipsychotics versus placebo for treating BPD using RCTs
<table>
<tr><th>Outcome</th><th>No. of studies</th><th>No. of patients</th><th>Effect size, SMD (95% CI), P value</th><th>Heterogeneity, I^2</th></tr>
<tr><td>Affective dysregulation: anger*</td><td>8 (FGA [H=2], SGA [A=1, O=4, Z=1])</td><td>1224</td><td>0.39 (0.18, 0.60), P= 0.0003</td><td>56%</td></tr>
<tr><td>Impulsive Behavioral Dyscontrol†</td><td>9 (FGA [H=2], SGA [A=1, O=5, Z=1)]</td><td>1284</td><td>0.19 (-0.01, 0.38), P = 0.05</td><td>52%</td></tr>
<tr><td colspan="5">*Anger was assessed using various tools: subscale Appropriate Anger of the CGI-BPD; subscales State Anger, Trait Anger, and Anger-in of the State-Trait Anger Expression Inventory; subscalesHostility of the SCL-90, subscale Indirect of the Buss-Durkee Hostility Inventory; subscales Excitement and Hostile Belligerence of the IMRS; subscale Irritability of the Overt Aggression scale-Modified; subscale Intense Anger of the ZAN-BPD.

†Impulsive behavioral dyscontrol was assessed using various tools: subscales Impulsivity and Recurrent Suicidality of the CGI-BPD; subscales Anger Out and Anger Control of the State-Trait Anger Expression Inventory; the Ward Scale of Impulse Action Patterns, the Barratt Impulsiveness Scale version II; Self-report Test of Impulse Control; the Buss-Durkee Hostility Inventory; the Overt Aggression scale-Modified; and the Impulsivity total score on the ZAN-BPD.</td></tr>
</table>
Adverse effects: Treatment related adverse events were not mentioned.

Authors' Conclusion:
"….At short term, antipsychotics can have significant effects on cognitive-perceptual symptoms, anger, and mood lability, but the wide and long-term use of antipsychotics in these patients remains controversial….." p.489
</td></tr>
<tr><td>Vita,[2,13,14] 2011, Italy</td><td>
Main Findings:
1. Comparison of antipsychotics versus placebo for treating BPD using RCTs
<table>
<tr><th>Outcome</th><th>No. of studies</th><th>No. of patients</th><th>Effect size, Hedges g (95% CI), P value</th><th>Heterogeneity, P value</th></tr>
<tr><td>Affective dysregulation*</td><td>4 (SGA [A=1,O = 2, Z =1])</td><td>461</td><td>-0.27 (-0.45, -0.09), P = 0.004</td><td>NS</td></tr>
<tr><td>Impulsive Behavioral Dyscontrol†</td><td>5 (FGA [H = 2], SGA [O = 2, Z =1])</td><td>254</td><td>-0.43 (-0.67, -0.18), P = 0.001</td><td>NS</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>
*Affective dysregulation was assessed using various tools: CGI –BPD (affective instability subitem), OAS-M (irritability sub-item), and STAXY (state anger sub-item)

†Impulsive behavioral dyscontrol was assessed using various tools: CGI-BPD (impulsivity sub-item), BIS, WSIA or behavioral report (recorded episodes of impulsivity and aggressive behavior)

2. Comparison of antipsychotics versus placebo for treating BPD using open-label studies (before and after treatment)
<table>
<tr><th>Outcome</th><th>No. of studies</th><th>No. of patients</th><th>Effect size, Hedges g (95% CI), P value</th><th>Heterogeneity, P value</th></tr>
<tr><td>Affective dysregulation*</td><td>4 (FGA = 1, SGA = 3)</td><td>57</td><td>-0.88 (-1.18, -0.58), P <0.001</td><td>NS</td></tr>
<tr><td>Impulsive Behavioral Dyscontrol†</td><td>15 (FGA [F =1, T = 1] , SGA [A =1, C =3, O = 2, Q = 6, R = 1])</td><td>239</td><td>-1.07 (-1.37, -0.76), P <0.001</td><td><0.001</td></tr>
<tr><td colspan="5">*Affective dysregulation was assessed using various tools: BPDSI (affective instability sub-item), CGI modified (anger sub-item), DIB (affective sub-item) and STAXY (state anger subitem)

†Impulsive behavioral dyscontrol was assessed using various tools: BIS, CGI modified (impulsivitysubitem), DIB (affective sub-item), WSIA, BPDSI (impulsivity sub-item), Buss Durk Hostility Inventory, BPRS (hostility sub-item) or behavioral report (recorded episodes of impulsivity and aggressive behavior)</td></tr>
</table>

Adverse effect: There was no significant difference in early discontinuation due to adverse events between patients on antipsychotics versus those on placebo.
</td></tr>
<tr><td></td><td>Authors' Conclusion:
"In conclusion, the efficacy of pharmacological treatment on the symptom dimensions of BPD has been shown by various independent meta-analyses, with a positive effect of drug treatment on the core symptoms of BPD…." P. 613</td></tr>
<tr><td>Stoffers,[3] 2010, Germany. (Cochrane review)</td><td>
Main Findings:
1. Comparison of antipsychotics versus placebo for treating BPD using RCTs
<table>
<tr><th>Outcome</th><th>No. of studies</th><th>No. of patients</th><th>Effect size, SMD (95% CI), P value</th><th>Heterogeneity, I^2</th></tr>
<tr><td>Anger</td><td>2 (FGA [H = 2])</td><td>114</td><td>-0.46 (-0.84, -0.09)*, P = 0.015</td><td>0%</td></tr>
<tr><td></td><td>1 (SGA [A= 1])</td><td>52</td><td>-1.14 (-1.73, -0.55)*,</td><td>NA</td></tr>
<tr><td></td><td>1 (SGA [Z = 1])</td><td>60</td><td>0.08 (-0.43, 0.58)*</td><td>NA</td></tr>
<tr><td></td><td>1 (FGA [T = 1])</td><td>50</td><td>-0.07 (-0.63, 0.48)†</td><td>NA</td></tr>
<tr><td></td><td>3 (SGA [O= 3])</td><td>631</td><td>-0.27 (-0.43, -0.12)‡,</td><td>0%</td></tr>
</table>
</td></tr>
</table>

First Author, Publication Year, Country	Main Findings and Authors' Conclusion

			P = 0.0007	
Impulsivity	2 (FGA [H = 2])	114	0.07 (-0.30, 0.43)*, P = 0.73	0%
	1 (SGA [A= 1])	52	-1.84 (-2.49, -1.18)*	NA
	1 (SGA [O = 1])	60	-0.04 (-0.54, 0.47)*	NA
	1 (SGA [Z = 1])	60	0.03 (-0.48, 0.53)*	NA
	2 (SGA [O = 2])	340	-0.18 (-0.40, 0.03)‡, P = 0.09	0%
	1 (SGA [O = 1])	291	-0.10 (-0.40, 0.20)**	NA

*SMD calculated on the basis of post-treatment results.
†SMD calculated on the basis of post-treatment means and pre-treatment SD
‡SMD calculated on the basis of change from baseline
** mean change difference (MCD)

Anger was assessed using various tools: SCL-90-HOS, BDHI, HSCL-HOS, SCL-90-R-HOS, STAXI-trait, STAXI-state, STAXI-anger, CGI-BPD-anger, CGI-inappropriate anger, OAS-M, OAS-M-irritability, AIAQ, ZAN-BPD-intense anger

Impulsivity was assessed using various tools: BIS, WSIA,STAXI-OUT, CGI-BPD (impulsivity), CGI (impulsivity), ZAN-BPD (impulsivity), OAS-M (aggression) or behavioral report (recorded episodes of impulsivity and aggressive behavior)

2. Comparison of adverse effects with antipsychotics versus placebo for treating BPD using RCTs

Outcome	No. of studies	No. of patients	Effect size, RR or SMD (95% CI), P value	Heterogeneity, P value
Any AE	2 (SGA [O = 2])	615	RR 1.13 (1.00, 1.28), P = 0.05	0%
	1 (SGA [Z = 1])	60	RR 2.75 (0.99, 7.68)	NA
Weight change	1 (FGA [H = 1])	58	SMD -0.18 (-0.70, 0.34),	NA
	6 (SGA [O = 6])	752	SMD 1.05 (0.90, 1.20), P < 0.00001	0%
Increased appetite	2 (SGA [O = 2])	615	RR 2.76 (1.75, 4.34), P = 0.00001	0%
Somnolence	2 (SGA [O = 2])	615	RR 2.76 (1.75, 5.03), P = 0.00005	0%
Dry mouth	2 (SGA [O =	615	RR	0%

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>2])</td><td></td><td>2.24 (1.08, 4.67), P = 0.03</td><td></td></tr>
<tr><td colspan="5">For antipsychotics compared to placebo, there were no statistically significant differences in other adverse effects such as headache, dizziness, disturbance in attention, fatigue, insomnia, nausea, and constipation</td></tr>
</table>

Authors' Conclusion:
"The available evidence indicates some beneficial effects with second-generation antipsychotics, mood stabilisers, and dietary supplementation by omega-3 fatty acids. However, these are mostly based on single study effect estimates. …Total BPD severity was not significantly influenced by any drug. No promising results are available for the core BPD symptoms of chronic feelings of emptiness, identity disturbance and abandonment. Conclusions have to be drawn carefully in the light of several limitations of the RCT evidence that constrain applicability to everyday clinical settings (among others, patients' characteristics and duration of interventions and observation periods)." P. 2</td></tr>
<tr><td>Mercer,[10] 2009, Canada</td><td>Main Findings:

Comparison of antipsychotics versus placebo for treating BPD using RCTs
<table>
<tr><th>Outcome</th><th>No. of studies</th><th>No. of patients</th><th>Effect size, g (95% CI), P value</th><th>Heterogeneity</th></tr>
<tr><td>Anger/ aggression</td><td>7 (FGA [Tpz = 1, H = 2], SGA [O = 3, A = 1])</td><td>319</td><td>-0.59 (-1.04, -0.15), P < 0.01</td><td>NR</td></tr>
<tr><td colspan="5">Anger was assessed using various tools: CGI-iBPD-nappropriate anger, CGI- anger physician, STAXI-anger out, SCL-90-hostility, SCL-90-anger/hostility, or or behavioral report (recorded episodes of impulsivity and aggressive behavior)</td></tr>
</table>

Adverse effect: Details were not provided but it was mentioned that one of the studies on haloperidol showed significant worsening of depressive symptoms.

Authors' Conclusion:
"This meta-analysis suggests that as a class, antipsychotics have a medium effect on anger in BPD in the short and medium term. …
While our meta-analysis also suggests that that typical antipsychotics are effective for anger, caution is advised as these studies were of short duration (5 and 6 weeks)… " P. 162-163</td></tr>
<tr><td colspan="2">A = aripiprazole, AE = adverse effect, BPD = borderline personality disorder, CI = confidence interval, H = haloperidol, NA = not applicable, NR = not reported, NS = not significant, O = olanzapine, Q = quetiapine, RR = relative risk, SD = standard deviation, SMD = standardized mean difference, T = thiothixene, Tpz = trifluoperazine, Z = ziprasidone,</td></tr>
</table>

APPENDIX 6: Guidelines and Recommendations

Guideline Society, Author, Country, Year	Recommendations
NICE,[12] UK, 2009	"Drug treatment should not be used specifically for borderline personality disorder or for the individual symptoms or behaviour associated with the disorder (for example, repeated self-harm, marked emotional instability, risk-taking behaviour and transient psychotic symptoms). Antipsychotics drugs should not be used for the medium- and long-term treatment of borderline personality disorder." P. 384
WFSBP,[11] Herpertz, Germany, 2007	"…..it may be recommended that a drug should be tried for at least 3 months with a sufficient baseline assessment of psychopathology, clearly defined targets of therapy and cessation of the drug if there is no benefit. …..Patients with BPD should be informed that there is no strong evidence base for the prescription of any drug. However, the off-label use of psychotropic agents may help individuals with BPD to improve affective symptoms and impulsivity. A pharmacological treatment might also be indicated in severe conditions to support psychosocial interventions or even to make them possible although there is not much of an evidence-base on when/how to combine pharmacotherapy/psychotherapy. Since pharmacotherapy will be part of a multimodal treatment programme including individual and/or group psychotherapy, psychotherapeutic specialists on these disorders should usually be involved rather early on." P. 214
BPD = borderline personality disorder, NICE = National Institute of Clinical Excellence, UK = United Kingdom, WFSBP = World Federation of Societies of Biological Psychiatry	