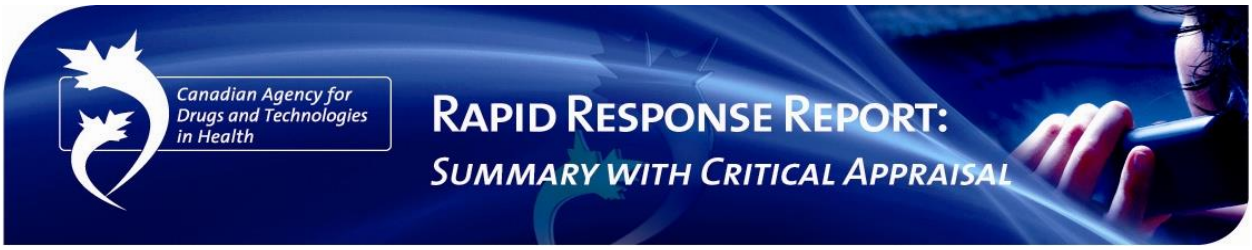

TITLE: Aripiprazole for Borderline Personality Disorder: A Review of the Clinical Effectiveness

DATE: 03 February 2017

Borderline personality disorder (BPD) is characterized by unstable interpersonal relationships, emotion and self-image, as well as marked impulsivity causing significant impairment.[1] The term BPD describes a disease in the "borderline" between psychosis and neurosis.[2] In the United States, it was reported in 2008 that the estimated prevalence was 1.4 percent in general population,[1] but may be as high as 20% among psychiatry inpatients. BPD is predominantly (75%) diagnosed in women in clinical settings.[1,2] However, there is no significant difference in the lifetime prevalence of BPD between men and women. This discrepancy of gender prevalence suggests that women with BPD are more likely to seek treatment than men.[1] Co-morbidity with other psychiatric disorders is common in patients with BPD, especially with mood, anxiety, substance-use, and eating disorders. The cause of BPD is not known. Most hypotheses suggest that BPD is due to a combination of genetic, biologic, and psychosocial factors.[1] Patients may experience spontaneous intermittent remission clinically sometimes. It is estimated that about 60% to 78% of BPD patients make suicide attempts, but the rate of completed suicides was found to be about 4% during a 10-years follow-up. An estimated lifetime risk of suicide of patients with BPD ranged from 3% to 10 %.[2] The clinical diagnosis of BPD is based on a comprehensive psychiatric assessment. Clinicians use all available sources of information to make the diagnosis including the patient's self-reported clinical history, the clinician's observations during interviews, and information from family, friends, and medical records. Children or young adolescents are generally not diagnosed with BPD.[1,3]

The first-line treatment for BPD is psychotherapy.[3] Pharmacotherapy is usually used as adjuncts to psychotherapy for treatment specific BPD symptoms clinically.[3] The medications used for BPD include antipsychotics, mood stabilizer, and antidepressants.[3]
It has been observed that pharmacotherapy only partially reduces symptoms, including lability, inappropriate anger, dysphoria, impulsivity, aggression towards self and others, dissociation, disturbed identity, paranoia and interpersonal problems.[1] Little published data indicates how long an effective medication for BPD should be continued.[3] Antipsychotics have been found to reduce BPD symptoms including aripiprazole (mean daily dose: 15 mg); ziprasidone (mean daily dose: 20 to 80 mg), olanzapine (mean daily dose: 5 to 9 mg, daily dose range 5 to 20 mg),

haloperidol (mean daily dose 5 mg, daily dose range 4 to 16 mg), Quetiapine XL (at a daily dose of 150 mg).[3]

Aripiprazole is indicated for the treatment of schizophrenia and related psychotic disorders in adults.[4] In the literature, it is indicated that, in the United States, the Food and Drug Administration (FDA) has not approved any medications for treatment of BPD.[3] Aripiprazole is not currently approved by the FDA[3] or Health Canada[4] for the treatment of BPD. The empirically use of antipsychotics in patients with BPD are considered as off-label use.[3,5] In the literature, it has been reported that clinical trials have not been adequate to examine the efficacy of antipsychotics in BPD.[3] Results have been variable and inconclusive. This document aims to review the clinical effectiveness and safety profile of aripiprazole in the treatment of patients with BPD.

RESEARCH QUESTION

What is the clinical effectiveness of aripiprazole for the treatment of borderline personality disorder?

KEY FINDINGS

The findings observed in two relatively small RCTs indicated that aripiprazole appears to be a safe and effective agent in the long term treatment of patients with borderline personality disorder. Similar clinical effectiveness and safety profiles were reported comparing aripiprazole with olanzapine in the treatment of BPD. However, due to the methodological limitations of the study design, whether the findings reported in the included RCTs could be generalized to Canadian routine clinical practice settings is uncertain and should be interpreted with caution.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed; Medline, Embase and PsychINFO via Ovid; The Cochrane Library; 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. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and January 5, 2017.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria	
Population	Adults with borderline personality disorder
Intervention	Aripiprazole (Abilify)
Comparator	Placebo, no treatment, other active comparators (e.g. other antipsychotics, mood stabilizers, anticonvulsants and antidepressants)
Outcomes	Clinical effectiveness (e.g. symptom reduction, quality of life), safety and harms
Study Designs	Health Technology Assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs).

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1 above, or they were duplicate publications (i.e. SRs/MAs reporting the same RCT results or the same RCT published in different journals).

Critical Appraisal of Individual Studies

The methodological quality of the included RCTs was assessed with Scottish Intercollegiate Guidelines Network, Methodology checklist 2 (SIGN 50 Check list 2).[6] The strengths and limitations of each included study were summarized and described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 90 citations were identified in the literature search. Following screening of titles and abstracts, 78 citations were excluded and 12 potentially relevant reports from the electronic search were retrieved for full-text review. Four more potentially relevant publications were retrieved from reference lists of relevant SRs. Therefore, a total of 16 potential relevant full-text articles were further reviewed. Of the 16 potentially relevant articles, four articles[7-10] based on two unique RCTs were found to meet the inclusion criteria. Six SRs/MAs[2,11-15] based on comprehensive literature searches also appeared to meet the inclusion criteria, however all six SRs/MAs included the same single RCT (Nickel 2006)[9] relevant to the current review. Therefore, in this review, only the original RCT(Nickel 2006)[9] is reviewed rather than the six SRs/MAs,[2,11-15] which are excluded as duplicate data. Overall four publications summarizing two RCTs[7-10] met the inclusion criteria and are included in this report. One RCT by Shafti et al. was reported in two publications;[7,8] the other RCT by Nickel et al. was reported in two publications including one follow-up article.[9,10] A total of 12 publications were excluded for various reasons. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

The key characteristics of the included two RCTs are summarized in Appendix 2, Table A2.

Study Design
One RCT identified was double-blind for eight weeks[9] with an 18-month open-label follow-up period[10] and the other RCT was an 8-week open-label design.[7,8] The patients in both RCTs

were randomized in a 1:1 ratio into intervention (aripiprazole) and the control groups respectively.

Country of Origin

One RCT was conducted in Austria[9,10] and the other was conducted in Iran.[7,8] No studies conducted in North America were identified.

Patient Population

One RCT[7,8] included 24 female inpatients diagnosed with BPD based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR) criteria. The mean age was 26 and 28 years old in the olanzapine and aripiprazole groups, respectively. Patients were excluded if they had co-morbid mental health conditions including major depressive disorder, bipolar disorder, psychosis or substance dependency in Axis I, mental retardation in Axis II, or identifiable neurological morbidity in Axis III. In the other RCT,[9] 52 patients diagnosed with BPD (DSM-IV/DSM-III-R) were included. The mean age was 21 and 22 years old in the aripiprazole and placebo groups, respectively; 83% were female. Patients were excluded if they were identified with schizophrenia, pregnancy, current suicidal ideation, or current severe somatic illness.

Interventions and Comparators

In the RCT by Shafti,[7,8] patients were randomized in 1:1 ratio to aripiprazole (N=12) and olanzapine (N=12). The mean modal doses for aripiprazole and olanzapine were 7.1 mg (SD: 2.6) per day and 6.5 mg (SD: 2.7 mg) per day, respectively. The duration was eight weeks. In the study by Nickel,[9] patients were randomized in 1:1 ratio to aripiprazole (N=26) and matching placebo arms (N=26). The mean modal dose for aripiprazole was 15mg per day. The patients were treated for 8 weeks in a double blind manner and continued to receive their original assigned treatment for another 18 months in an open label observational manner to assess the long-term effect and safety of aripiprazole in the treatment of BPD.

Outcomes

In the RCT by Shafti,[7,8] outcomes assessed included the Brief Psychiatric Rating Scale (BPRS) for estimation of baseline psychopathology, clinical outcome and treatment response; the Buss-Durkee Hostility Inventory (BDHI) for the assessment of anger& hostility, and the Clinical Global Impressions-Severity Scale (CGI-S) for assessment of overall illness severity. In the RCT by Nickel,[9] changes in scores on the symptom checklist (SCL-90-R), the Hamilton Depression Rating Scale (HAM-D), the Hamilton Anxiety Rating Scale (HAM-A), and the State-Trait Anger Expression Inventory. Side effects were also assessed.[9]

Summary of Critical Appraisal

The strengths and limitations of the methodological quality are summarized in Appendix 3, Table A3. The research objectives were clearly reported in both RCTs.[7-10] Diagnosis of patients with BPD was based on the DSM-IV-TR in the study by Shafti[7,8] or DSM-IV/DSM-III-R criteria in the study by Nickel.[9] Patient baseline characteristics were briefly described and were reportedly similar between the two groups in both RCTs.[7-9] The RCT by Nickel[9] was a double-blind study and the allocation concealment was well described. The outcome measurements in both RCTs

were standard, reliable and widely accepted. No dropouts were reported and all patients were included in the analysis (intention to treat analysis). No conflicts of interest were reported in either of the RCTs.[7-10] The key limitations were as follows: 1) the method of how the patient was randomized (e.g. based on computer generated randomization or based on randomization table) was not described; 2) the study by Shafti[7,8] was an open-label RCT; 3) in addition, the blinding of outcome assessors was not described in the RCT by Nickel;[9,10] 4), use of concomitant drugs was not well reported in either of the studies, and whether only difference between the groups was the treatment under investigation was not clearly reported; 5) Neither RCT was conducted in multiple research sites and both included a relatively small number of patients. The study durations (8-weeks) were relatively short. It is not clear how well the findings from the RCTs can be generalized to routine clinical practice since most patients with comorbid diseases and patients with suicidality.

Summary of Findings

What is the clinical effectiveness of aripiprazole for the treatment of borderline personality disorder?

Aripiprazole versus olanzapine

One small open-label RCT (n=24) evaluated the effects of aripiprazole and olanzapine in the treatment of female patients with BPD. The main results reported are summarized in Appendix 4, Table A4. It was found that both aripiprazole (7.1 mg per day) and olanzapine (5.5 mg per day) showed a statistically significant improvement in BPRS at the end of eight-week treatment ($P = 0.01$ and $P = 0.04$ for aripiprazole and olanzapine, respectively).[7,8] The mean total scores of the BPRS were reduced (lower score of BPRS indicates clinical improvement) by approximately 19% and 26% in the aripiprazole and olanzapine groups, respectively.[8] The mean total score of the BDHI improved (lower score of BDHI indicates clinical improvement) by approximately 12% with aripiprazole ($P < 0.06$, not statistically significant) and improved 15% with olanzapine ($P < 0.04$, statistically significant).[8] CGI-S improved (lower score of CGI-S indicates clinical improvement) statistically significantly with olanzapine (21%, $P = 0.03$) but not statistically significant with aripiprazole (19 %, $P = 0.07$).[7] Differences between olanzapine and aripiprazole were reported to be not statistically significant. The authors concluded that both aripiprazole and olanzapine had relatively similar clinical improvement on general symptoms of BPD.[7,8]

Aripiprazole versus placebo

One double blind RCT evaluated the relative effects of the aripiprazole (15 mg per day) with matching placebo in the treatment of patients with BPD. The main results reported are summarized in Appendix 4, Table A4, Table A5 and Table A6. Based on the intent-to-treat analysis, at the end of eight-week double blind RCT phase, this study reported a statistically significant improvement in scores on most scales of the SCL-90-R, as well as the HAM-D, the HAM-A, and all scales of the State-Trait Anger Expression Inventory in the patients treated with aripiprazole compared with placebo.

Similar adverse events including self-injury were observed in both groups. None of the AEs were considered as serious AEs. No suicidal acts or body weight changes were observed. The clinical comparative effectiveness and safety profile of aripiprazole compared to placebo were

maintained following an 18-month open-label treatment. The authors concluded that aripiprazole appears to be a safe and effective agent in the long-term treatment of patients with BPD.[9,10]

Limitations

Several key limitations were identified in the included two RCTs. The randomization method was not clearly described in either of the two RCTs. One RCT[7,8] was open label design. The blinding of outcome assessors was not described in the double blind RCT by Nickel.[9,10] No detailed baseline characteristics were reported in either of the two RCTs. Use of concomitant drugs during the study was not well reported. Therefore, whether the observed effects were confounded by other unknown factors cannot be well determined. In addition, the sample size of the both RCTs was relatively small. Each RCT was conducted in a single research site. The open label study was conducted in Iran and most patients with comorbid diseases and patients with suicidality were excluded in the included RCTs. Together, whether the findings observed in the two RCTs can be generalized to Canadian routine clinical practice is uncertain and should be interpreted with caution.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The findings observed in the two relative small RCTs indicated that aripiprazole appears to be a safe and effective agent in the long term treatment of patients with borderline personality disorder. Similar clinical effectiveness and safety profiles were reported comparing aripiprazole with olanzapine in the treatment of BPD. However, due to the methodological limitations of the study design or insufficient information reported in the available publications, whether the findings reported in the included RCTs could be generalized to Canadian routine clinical practice settings is uncertain and should be interpreted with caution. Well-designed double blind RCTs with more patient participation, longer trial duration, and conduced in North American settings are needed to fully evaluate the clinical effectiveness and safety profile of aripiprazole in the treatment of BPD.

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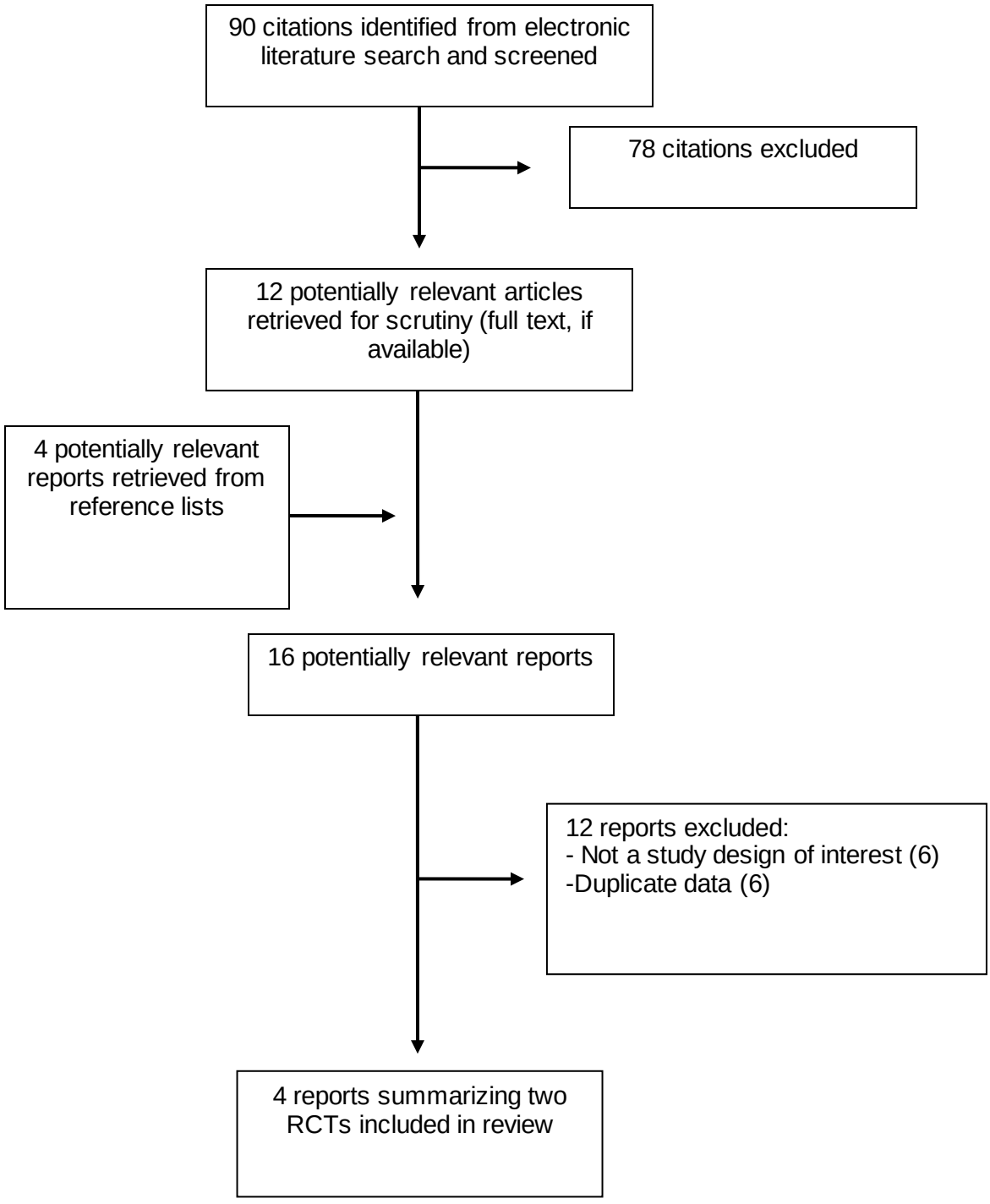
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A2: Characteristics of Included RCTs / Publications

First Author, Publication Year, Country	Study Design/ Length of Follow-dup	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
Shafti, 2015;[8] Shafti, 2014;[7] Iran	Open-label RCT 8 weeks 8 weeks	Female patients, with BPD (DSM-IV TR criteria) N=24, Age: mean(SD), years ARIP: 28.1±4.8 OLAN: 25.8± 3.6	ARIP Mean dose: 7.1 mg /day (SD: 2.6)	OLAN Mean dose: 6.5 mg /d (SD: 2.7)	BPRS BDHI CGI-S
Nickel, 2006;[9] Nickel, 2007;[10] Austria	DB RCT 8 weeks[9] with 18-month open-label treatment follow-up[10]	Patient with BPD (DSM-III R criteria) N = 52 Male: 17% Age: mean(SD), years ARIP: 22.1±3.4 PLO: 21.2± 4.6	ARIP 15 mg/day	PLC Matching placebo	HAM-D HAM-A STAEI SCL-90-R

AE = adverse event; ARIP = aripiprazole; BDHI = Buss-Durkee Hostility Inventory; BPD = borderline personality disorder; BPRS= CGI-S = Clinical Global Impressions-Severity Scale; DB = double blind; DSM-III R = Diagnostic and Statistical Manual of Mental Disorders, 3rd edition revision; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision criteria; HAM-A = the Hamilton Anxiety Rating Scale; HAM-D = the Hamilton Depression Rating Scale; OLAN = olanzapine; PLO=placebo; SCL-90-R = Symptom Checklist; RCTs=randomized control trials; SD = standard deviation; STAEI = The State-Trait Anger Expression Inventory.

APPENDIX 3: Summary of Study Strengths and Limitations

Table A3: Strengths and Limitations of included RCTs / Publications

First Author, Publication Year	Strengths	Limitations
RCT assessed with SIGN 50 Check list[6]		
Shafti, 2015;[8] Shafti, 2014;[7]	• Research question was clearly defined • Randomized allocation • Key patient characteristics at baseline are comparable between intervention and comparison groups • Only difference between groups is treatment under investigation • Outcome was standard, valid and reliable • No dropout • All patients were included in the analysis	• Randomization method was not clearly described • Open-label design • Detail baseline characteristics in the two arms were not well reported. • Use of concomitant drugs were not well reported • Small sample size and conducted in one research site
Nickel, 2006;[9] Nickel, 2007;[10]	• Research question was clearly defined • Randomized allocation • Double blind method • Allocation concealment was described • Key patient characteristics at baseline are reported. • Only difference between groups is treatment under investigation • Outcome was standard, valid and reliable • Dropout: in total, 5 out of 52 patients missed the evaluation in last two weeks (9.6%) • All patients were included in the analysis (Intention to treat)	• Randomization method was not clearly described • Blinding of outcome assessors were not described • Detail baseline characteristics in the two arms were not well reported. • Use of concomitant drugs were not well reported • Small sample size and conducted in one research site

RCT=randomized controlled trial;

APPENDIX 4: Main Study Findings and Authors' Conclusions

Table A4: Summary of Findings of included RCTs

First Author, Publication Year	Main Study Findings*	Author's Conclusions
Shafti, 2015;[8] Shafti, 2014;[7]	**BPRS** (Mean ± SD) ARIP: Baseline 44.1±10.7 Week 8: 35.8±9.7 Change from baseline: Mean (95%CI) , -8.3 (0.04, 16.5) , p =0.04; OLAN: Baseline 43.8± 11.3 Week 8: 32.5±9.6 Change from baseline: Mean (95%CI), -11.3 (2.4, 20.1) p =0.01; (ARIP – OLAN) at week 8 Mean (95%CI): 3.3 (-11.0, 4.4) P =0.8 **BDHI** (Mean ± SD) ARIP: Baseline 58.3 ±9.75 Week 8: 51.1±8.23 Change from baseline: Mean (95%CI), -7.2 (-0.48, 14.8), p =0.06; OLAN: Baseline 59.7±9.59 Week 8: 50.7±10.72 Change from baseline: Mean (95%CI), -9.0 (0.35, 17.57), p =0.04;[7] (ARIP – OLAN) at week 8 Mean (95%CI): -0.04 (-8.4, 7.6), p =0.1 **CGI-S**(Mean ± SD) ARIP: Baseline 3.4±0.91 Week 8: 2.7±0.78 Change from baseline: Mean (95%CI), -0.7(-0.07, 1.37), p =0.07; OLAN: Baseline: 3.6±0.64 Week 8: 2.8±0.96 Change from baseline: Mean (95%CI), -1.1(0.06, 1.44), p =0.03; (ARIP – OLAN) at week 8 Mean (95%CI): -0.1(-0.6, 0.8), p =0.3 ***AEs (n, number of patients with AEs)*** ARIP group: Tremor (n=1); Inner restless (n=2); akethesia (n=1); Headache (n=1) and Insomnia (n=1);	The author concluded that (on *page, 132*) "Both olanzapine and aripiprazole had relatively comparable effect on general symptoms of BPD, in spite of a bit greater influence of olanzapine on some of the secondary outcome measures.[7] (*on page 38*) "In spite of somewhat comparable effects, it seems that olanzapine, in comparison with aripiprazole, is more effective on borderline personality symptoms.[8]

Table A4: Summary of Findings of included RCTs		
First Author, Publication Year	**Main Study Findings***	**Author's Conclusions**
	OLAN group: Weight gain (n=3), somnolence (n=4), dizziness (n=2) and tremor (n=2) All above AEs were mild and well tolerated	
Nickel, 2006;[9] Nickel, 2007;[10]	(Detail see tables A5 and A6 below) At the end of DB RCT (at week 8) **ARIP – PLO,** (mean, 95%CI) HAM-D -4.9 (–6.5 to –2.1), P= 0.002 HAM-A -3.2 (–6.2 to –1.2), P= 0.007 State Anger -7.7 (–10.6 to –5.2), p <0.001 Trait Anger -5.9 (–9.3 to –3.7), p<0.001 Anger In -4.2 (–5.6 to –1.4), p=0.002 Anger Out -6.4 (–7.8 to –2.8), p <0.001 Anger Control 2.7 (2.1 to 3.9), P= 0.02 **Nine Scales and the Global Severity Scale (GSI) of the Symptom Checklist (SCL-90-R)** Somatization -2.9 (–8.2 to 1.0), p=0.15 Obsessive-Compulsiveness -3.4 (–8.0 to –2.4), P=0.01 Insecurity in Social Contacts -4.5 (–8.0 to –2.8), P<0.001 Depression -16.4 (–20.9 to –13.7), P<0.001 Anxiety -9.1 (–9.9 to –4.7), P<0.001 Aggressiveness/Hostility -8.5 (–11.7 to –6.7), p<0.001 Phobic Anxiety -5.7 (–10.9 to –3.9), p<0.001 Paranoid Thinking -8.1(–10.3 to –3.5), P <0.001	The author concluded that (on *page, 833*)[9]: Aripiprazole appears to be a safe and effective agent in the treatment of patients with borderline personality disorder,[9] and (on page 191)[10] "Aripiprazole appears to be an effective and relatively safe agent in the long-term treatment of patients with BPD."[10]

Table A4: Summary of Findings of included RCTs		
First Author, Publication Year	**Main Study Findings***	**Author's Conclusions**
	Psychoticism -6.2 (–6.9 to –1.3), P= 0.02 GSI -9.3 (–13.2 to –7.0), p<0.001 AE: no usable data for ARIP(p.34)[9] **Findings reported for 18-month follow-up period.** ● SCL-90-R scales: the patients in ARIP group experienced significantly greater improvement than that in the PLO group on all SCL-90-R scales. ●Self-injury: *8 weeks before therapy:* ARIP: 7:26 versus PLO, 5:26; *During the 8 weeks of therapy (RCT phase):* ARIP: 2:26 versus PLO 7:26; *During the 18-month follow-up phase*: ARIP: 4:26 versus PLO: 11:26, (less in the ARIP group) ●Two patients in the PLO attempted suicide. ●No SAE observed during the follow-up ●No significant weight change was observed.	

ARIP = aripiprazole; BDHI = Buss-Durkee Hostility Inventory; BPD = borderline personality disorder; BPRS= CGI-S = Clinical Global Impressions-Severity Scale; CI = conference interval; DB = double blind; DSM-III R = Diagnostic and Statistical Manual of Mental Disorders, 3rd edition revision; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision criteria; HAM-A = the Hamilton Anxiety Rating Scale; HAM-D = the Hamilton Depression Rating Scale; OLAN = olanzapine; PLO=placebo; SCL-90-R = Symptom Checklist; RCTs=randomized control trials; SAE: serious adverse events; SD = standard deviation; STAEI = The State-Trait Anger Expression Inventory.

*Note: For study by Shafti,[7,8] all intragroup mean difference (change from baseline) and between group mean difference at week 8 (ARIP – OLAN) were not reported by the authors and therefore calculated by CADTH. For study by Nickel,[9] all between group mean differences at week 8 (ARIP – PLO) were not reported by the authors and therefore calculated by CADTH.

Table A5: Nine Scales and the GSI of the SCL-90-R reported in RCT by Nickel 2006 [9]

	Outcomes (Mean±SD)									
	Somatization	**OC**	**Insecurity in Social Contacts**	**Depression**	**Anxiety**	**AH**	**Phobic Anxiety**	**Paranoid Thinking**	**Psychoticism**	**GSS**
Baseline										
ARIP group (N=26)	69.5±9.1	60.1±6.4	68.2±6.9	77.4±8.6	72.3±6.4	78.6± 4.4	72.1± 7.6	69.9± 8.2	60.5± 7.6	75.1± 7.1
PLO group (N=26)	68.8±8.7	58.3±7.5	67.3±5.7	76.5±9.2	74.1±5.9	77.9± 3.9	70.4± 8.3	71.1± 8.6	62.6± 7.9	74.3± 8.2
At Week 8										
ARIP group (N=26)	62.5±7.3	55.2±4.3	59.7±5.3	56.8±6.6	61.1±5.2	64.6±6.8	61.4± 7.4	60.2± 5.1	54.3± 3.5	60.1± 4.2
PLO group (N=26)	65.4±8.9	58.6±7.9	64.2±6.2	73.2±9.6	70.2±7.3	73.1± 7.8	67.1± 9.5	68.3± 9.4	60.5± 6.2	69.4 ±9.3
Mean Diff at week 8 (ARIP – PLO)[a] (95%CI), p value[b]	*-2.9* (–8.2 to 1.0); p=0.15	*-3.4* (–8.0 to –2.4) p=0.01	*-4.5* (–8.0 to –2.8) p<0.001	*-16.4* (–20.9 to –13.7) p<0.001	*-9.1* (–9.9 to –4.7) p<0.001	*-8.5* (–11.7 to – 6.7) p<0.001	-5.7 (–10.9 to –3.9) p<0.001	-8.1 (–10.3 to –3.5) p <0.001	-6.2 (–6.9 to –1.3) p= 0.02	-9.3 (–13.2 to –7.0) p<0.001

AH = aggressiveness/ hostility; ARIP = aripiprazole; CI = conference interval; Diff = difference; GSS = global severity scale; OC = obsessive-compulsiveness; PLO = placebo; SD = standard deviation. SCL-90-R = Symptom Checklist.

[a] Difference in change in score between groups. Between group mean difference was calculated by CADTH, 95%CI of the mean difference and p value were reported by the author[9,10]

[b] Probability of error (Mann-Whitney U test).

Note: For study by Nickel,[9] all between group mean differences at week 8 (ARIP – PLO) were not reported by the authors and therefore calculated by CADTH.

Table A6: Detailed results (2) reported in RCT by Nickel 2006 [9]							
	Outcomes (Mean±SD)						
	HAM-D	HAM-A	State Anger	Trait Anger	Anger In	Anger Out	Anger Control
Baseline							
ARIP group (N=26)	20.3± 4.4	23.3± 4.1	32.1± 5.3	30.5± 6.4	24.5± 4.2	25.0± 5.7	18.9± 4.7
PLO group (N=26)	20.9± 3.9	22.8± 5.3	31.9± 5.9	29.9± 5.8	25.2± 4.8	26.1± 5.5	18.6± 5.3
Week 8							
ARIP group (N=26)	13.9± 2.8	16.3± 3.5	18.5 ±4.1	18.1± 3.0	16.3± 2.5	14.3± 2.6	22.1± 2.4
PLO group (N=26)	18.8± 4.7	19.5± 5.0	26.2± 4.4	24.0± 4.7	20.5± 3.3	20.7± 4.1	19.4± 5.1
Mean diff at week 8 (ARIP – PLO)[a] (95%CI), p value[b]	-4.9 (–6.5 to –2.1) p = 0.002	-3.2 (–6.2 to –1.2) p = 0.007	-7.7 (–10.6 to –5.2) p <0.001	-5.9 (–9.3 to –3.7) p<0.001	-4.2 (–5.6 to –1.4) p=0.002	-6.4 (–7.8 to –2.8) p <0.001	2.7 (2.1 to 3.9) p = 0.02

ARIP = aripiprazole; CI = conference interval; Diff = difference; PLO = placebo; SD = standard deviation.
[a] Difference in change in score between groups. Between group mean difference was calculated by CADTH, 95%CI of the mean difference and p value were reported by the author[9]
[b] Probability of error (Mann-Whitney U test).
Note: For study by Nickel,[9] all between group mean differences at week 8 (ARIP – PLO) were not reported by the authors and therefore calculated by CADTH