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SUMMARY WITH CRITICAL APPRAISAL

Electroconvulsive Therapy for the Treatment of the Behavioural and Psychological Symptoms of Dementia: A Review of Clinical Effectiveness and Guidelines

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

AD	Alzheimer disease
DLB	dementia with Lewy Bodies
ECT	electroconvulsive therapy
HDRS	Hamilton Depression Rating Scale
LBD	Lewy Body dementia
MADRS	Montgomery-Asperg Depression Rating Scale
MMSE	Mini Mental Status Exam
PD	Parkinson's disease
PDD	dementia associated with Parkinson's disease

Context and Policy Issues

Dementia refers to a state of cognitive impairment in the presence of impaired language or physical function that cannot be attributed to delirium or any other medical, neurological or psychiatric condition.[1] Dementia manifests in a variety of forms, namely, Alzheimer disease (AD), frontotemporal dementia, frontotemporal lobar dementia, Lewy Body dementia (LBD) or dementia with Lewy Bodies (DLB), vascular dementia, and dementia associated with Parkinson's disease (PDD).[1] Commonly observed and often overlapping symptoms of the various forms of dementia include deterioration in memory and adverse changes in mood, behaviour, communication, judgement and reasoning.[1,2] An estimated 402,000 Canadians aged 65 years and older are living with dementia, with this number expected to increase as the population ages and expands.[2]

Treatment options for symptoms of dementia include, but are not limited to, antipsychotics, antidepressants, carer education, psychological interventions, physical exercise, gait cueing, environmental modification, music, simulated presence, occupational therapy, physical therapy, transcranial magnetic stimulation, transcranial direct current stimulation, deep brain stimulation, and electroconvulsive therapy (ECT).[3]

ECT refers to the use of short pulses (i.e., pulses lasting less than 2 milliseconds) of electricity to produce a generalized seizure in a symptomatic patient.[3] The impetus for using ECT as a potential treatment option for dementia comes from past observations of positive outcomes in patients with severe psychiatric disorders ranging from schizophrenia to major depressive disorder.[3] Concerns remain however, about adverse effects of ECT and the probability of relapse in those who respond to the treatment.[4]

This review aims to summarize published evidence regarding the clinical effectiveness and safety of ECT for the treatment of the behavioural and psychological symptoms of dementia in older patients, along with relevant guidelines.

Research Questions

1. What is the clinical effectiveness of electroconvulsive therapy for the treatment of the behavioural and psychological symptoms of dementia in older adults?
2. What is the safety of electroconvulsive therapy for older adults with dementia?
3. What are the evidence-based guidelines regarding the use of electroconvulsive therapy for the treatment of the behavioural and psychological symptoms of dementia in older adults?

Key Findings

Five systematic reviews were identified that addressed the clinical effectiveness and safety of electroconvulsive therapy (ECT) in treating older patients with dementia. Due to the paucity and low quality of the primary evidence that was found, caution must be taken in making inferences from the results. The systematic reviews included primarily chart reviews, case series and case reports published between 1975 and 2017. There was considerable heterogeneity in the patient populations, the components of the intervention, and the types of outcomes that were included in the studies.

Each of the systematic reviews reported on a subset of the outcomes of interest. Evidence of limited quality and quantity suggested that the impact of ECT on depressive and psychotic symptoms was mixed and the effects were not permanent. There were reports of reductions in the intensity of visual hallucinations, delusions and other neuropsychiatric symptoms in a subset of patients with LBD or DLB, reductions in agitation and aggression in patients with mild to severe dementia, and clinically significant improvement in symptoms of mania and agitation following a short course of ECT and bi-weekly maintenance treatments. The impact on cognition was mixed with three reviews reporting that some patients exhibited symptoms of confusion and other forms of cognitive decline while other patients showed signs of improvement. Data from three reviews suggested that patients relapsed between one week and 5 years of being treated with ECT.

Coupled with the mixed and transient responses to ECT were reports of safety issues, ranging from delirium, seizures, stuttering and slurred speech to serious cardiovascular events. It was unclear whether certain events such as spontaneous seizures and confusion could be attributed to treatment or the prevailing condition of the patients. No relevant evidence-based guidelines were found that addressed the use of ECT for the treatment of the behavioural and psychological symptoms of dementia in older adults.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Ovid Medline, PsycINFO, the Cochrane Library, Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were electroconvulsive therapy and dementia. Search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and April 23, 2019.

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	Q1 and Q3 - Older adults with behavioural and psychological symptoms of advanced dementia Q2 – Older adults with dementia
Intervention	Electroconvulsive therapy; electroshock therapy with or without other primary or adjunct treatments
Comparator	Usual care; Sham stimulation; Any active treatment (e.g., antipsychotic drugs; physical restraints; environmental and behavioural therapies); Before and after
Outcomes	Q1 – Effectiveness in reducing behavioural and psychological symptoms of dementia (e.g. agitation, aggression, confusion, insomnia, anxiety, psychomotor agitation, depression, cognitive function) Q2 – Safety – particular concerns include cardiac events and disorientation Q3 – Guidelines regarding the use of electroconvulsive therapy for people with dementia; patient selection; patient contraindications

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, if they were duplicates or if they were published prior to 2014. Guidelines without evidence of a systematic literature search or those that reported on ECT without focusing on patients with dementia were also excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using the AMSTAR 2.[5] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 350 citations were identified in the literature search. Following screening of titles and abstracts, 328 citations were excluded and 22 potentially relevant reports from the electronic search were retrieved for full-text review. Thirty-two potentially relevant publications were retrieved from the grey literature search and other sources for full text review. Of these 54 potentially relevant articles, 49 publications were excluded for various reasons, and 5 publications met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA[6] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 6.

Summary of Study Characteristics

Study characteristics are summarized below and details are available in Appendix 2.

Study Design

Five systematic reviews were included in this review.[7-11] One of each was published in 2014,[7] 2016,[8] and 2017,[9] and two were published in 2018.[10,11] The reviews included

primarily chart reviews, case series and case reports published between 1975 and 2017.[7-11] Five primary studies were included in multiple reviews. Table 5 in Appendix 5 provides a detailed description of the overlap in the primary studies between the systematic reviews. All of the studies in two of the five systematic reviews met the inclusion criteria of this report.[8,11] Each of the three remaining reviews had a more extensive scope, with two out of their 15 included studies,[10] four out of 21 studies,[9] and 13 out of 43 studies,[7] meeting the inclusion criteria of this report. The relevant outcomes of interest were extracted.

Country of Origin

The systematic reviews were published by authors in Australia and the United Kingdom,[9] Canada,[7] the Netherlands,[11] the United Kingdom,[10] and the United States.[8]

Patient Population

The studies enrolled 37 adults with LBD or DLB,[9,10] 122 with dementia accompanied by agitation and aggression,[11] 116 with Parkinson's disease (PD) and comorbid depression,[8] or 146 with dementia with or without depression.[7] Data from patients with other conditions that were included in the reviews were not incorporated into this report. Commonly reported problem behaviours from patients were unspecified agitation, screaming, yelling, and physical aggression towards caregivers or others.[11] The settings in which patients were treated were not described. For those primary studies that reported the ages of patients that met the inclusion criteria, the minimum age was 51 years and the maximum was 97 years. The reviews did not consistently report on the sex of the patients who were enrolled.

Interventions and Comparators

The intervention of interest in all of the studies was ECT, however components of the treatment such as the stimulus dose and pulse width, placement of leads, the number of sessions, the duration of single sessions, and the length of treatment varied. For example, the pulse width ranged from ultra-brief (i.e., spanning 0.25 to 0.3 milliseconds[11]) or brief (i.e., spanning 0.5[7,8,11] to 1.0 milliseconds[11]) up to 1.6 ± 0.2 milliseconds.[8]

In the review involving patients with dementia who were being treated for agitation or aggression, the stimulus dose relative to the seizure threshold (ST) for bilateral treatment was just above ST in one study and 1.5 to 3 times above ST in three studies.[11] For right unilateral treatment, the treatment stimuli across four studies ranged from 4 to 6 times ST in four studies.[11] The review involving 22 patients with DLB reported that ECT was administered over seven sessions with unilateral lead placement in one case study, over six sessions with bifrontotemporal lead placement in one case series, mostly bilateral in a second case series, and unreported in a third case series.[9] The authors did not provide details about the stimulus dose and pulse width, the duration of single sessions, and the length of treatment. In the review involving patients diagnosed with PD and comorbid depression, a current of 0.8 amperes peak amplitude stimulus dose was used in two primary studies while the current was listed as 0.8 milliamperes in one study.[8] Researchers primarily used bilateral lead placement, rather than right unilateral placement of the ECT leads, despite the latter being recommended generally to prevent cognitive losses.[8] An average of 3 to 14 ECT sessions were administered.[8] In the review that enrolled patients with dementia both bilateral and unilateral ECT were administered and the number of sessions ranged from one to 23.[7] The review involving 15 patients with LBD or DLB did not provide details about the intervention.[10] All or a subset of enrolled patients were treated concurrently with medication or other non-medication based interventions.[10,11]

Outcomes

The relevant clinical outcomes of interest that were reported in the systematic reviews were:

- Treatment response rate[8,11]
- changes in depressive symptoms[8-10]
- changes in psychotic symptoms, agitation, aggression or other problem behaviour[9-11]
- changes in cognition[7-9]
- duration of treatment effect or time to relapse[7,8,11]

Four reviews also reported on safety outcomes (i.e., side effects or adverse events).[7-9,11]

The clinical outcomes were objectively measured with a variety of scales including but not limited to, the Alzheimer's Disease Cooperative Study Group-Activities of Daily Living (ADCS-ADL),[11] the Bush-Francis Catatonia Rating Scale (BFCRS),[11] the Clinical Global Impression (CGI),[11] the Cohen Mansfield Agitation Inventory (CMAI),[11] the Cornell Scale for Depression in Dementia (CSDD),[11] the Global Assessment of Functioning (GAF),[11] the Hamilton Depression Rating Scale (HDRS),[7-9] the Montgomery-Asperg Depression Rating Scale (MADRS),[7] the Mini Mental Status Exam (MMSE)[8,11] Neuropsychiatric Inventory Questionnaire (NPI-Q),[11] the Pittsburgh Agitation Scale (PAS),[11] and the Social Dysfunction and Aggression Scale (SDAS).[11] van den Berg et al. (2018) included one primary study that used an unpublished scale to assess clinical outcomes along with other studies that did not indicate how outcomes were measured.[11] Changes in the rating scale scores signified changes in clinical status.[11] For some scales, an increase in score signified clinical improvement while for others, a decrease in score was indicative of clinical improvement. The authors of the systematic reviews did not discuss how the various scales were validated. In an undisclosed number of studies researchers based treatment response on qualitative measures of changes in depressive and cognitive symptoms such as "modest or mild improvement" and "profound memory impairment".[8,11]

The quality and potential likelihood of bias of individual studies were assessed using the CARE criteria checklist for case reports,[10] the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies for trials,[9,10] and the National institute for Health and Care Excellence (NICE) Methodology Checklist for Qualitative Studies.[9] The body of evidence for each outcome was evaluated using guidelines from the Oxford center for Evidence-Based Medicine.[10] Three reviews did not report on the assessment of the quality of their included studies.[7,8,11]

Summary of Critical Appraisal

The critical appraisal of the studies is summarized below and details are available in Appendix 3.

Systematic Reviews

The systematic reviews[7-11] were critically appraised using AMSTAR 2.[5] Strengths common to the five reviews were that the populations and the interventions were described in the objectives, multiple databases were searched, keywords for the literature search and search strategies were provided, and the included studies were described in adequate detail. In three of the systematic reviews, study selection and data extraction were performed in duplicate.[8,9,11] Two systematic reviews gave an explicit statement that the methods were established prior to the conduct of the review and their authors also

assessed the quality of primary studies[9,10] and the overall level of evidence for each outcome of interest.[10] These strengths indicate that the authors mitigated bias in the selection and interpretation of primary studies.

Limitations common to the systematic reviews were that the authors did not provide a list of excluded studies, justification for the exclusion criteria, sources of funding for the primary studies, a description of the treatment setting, or a time-frame for follow-up.[7-11] In three reviews, at least one author had a potential conflict of interest through receipt of funding from a manufacturer of a relevant technology.[7,9,10] The authors' relationships with manufacturers could have influenced their interpretation of the primary studies and their reporting. Importantly, authors of some of the reviews did not critically assess the quality of the primary studies,[7,8,11] and did not critically assess the quality of the overall evidence of each outcome.[7-9,11] One patient who was diagnosed with bipolar mania and did not exhibit signs of depression was included in the population of adults with PD and comorbid depression, highlighting the heterogeneity of the clinical conditions that were included in the reviews.[8]

Summary of Findings

The main study findings are summarized below while details and authors' conclusions are provided in Appendix 4.

Clinical Effectiveness of ECT for the treatment of behavioural and psychological symptoms of dementia in older adults

Changes in depressive symptoms

Evidence from four systematic reviews reported positive outcomes from ECT. Eight patients with LBD or DLB experienced a statistically significant reduction in HDRS scores after being treated with bifrontotemporal ECT (at a pulse rate of 0.5 milliseconds).[7,9,10] Clinical symptoms of depression improved in two patients but in one of them the change was transient.[7,9,10] A review of a collection of case reports and case series reported that 93% of 116 adults who were diagnosed with PD and comorbid depression experienced an improvement.[8] A group of 31 hospitalized patients who had dementia and ranged in age from 55 to 97 years, experienced a statistically significant decline in their mean MADRS score over the course of one to 23 ECT sessions.[7] In addition, they experienced a statistically significant increase in their mean MMSE score of 1.6 points from a mean baseline score of 18.8±5.5.[7] These changes in MADRS and MMSE scores signified clinical improvement.[7]

Changes in cognition and confusion

Following ECT, some patients exhibited symptoms of confusion and other forms of cognitive decline.[7-9] Specifically, eight (67%) out of 12 hospitalized patients with AD experienced cognitive decline six weeks after ECT; the decline lasted for six months in four of the patients.[7] Twenty-eight (24%) out of 117 patients with PD and cobmorbid depression exhibited worse cognition[8] and two (29%) out of seven patients with DLB exhibited confusion immediately after ECT.[9] On the other hand, three patients in a different case series exhibited improvements in cognition following a short course of ECT and bi-weekly maintenance treatments.[7] In addition three (3%) out 117 patients across multiple studies exhibited improved symptoms of cognition.[8]

Changes in psychotic symptoms or problem behaviour

Reductions in the intensity of visual hallucinations, delusions and other neuropsychiatric symptoms were observed in three patients with LBD or DLB as reported in one case study and one case series of seven patients.[9,10] Hallucinations recurred in one out of the seven patients.[10] Across 17 primary studies, 107 (88%) out of 122 patients with dementia achieved substantial clinical reduction in agitation and aggression, cessation of yelling or screaming, and return to eating prior to their 5th ECT session.[11]

Three older patients, whose ages were not disclosed, demonstrated clinically significant improvement in symptoms of mania and agitation following a short course of ECT and bi-weekly maintenance treatments.[7] Additionally, a female patient with haloperidol-resistant vascular dementia and psychotic symptoms responded for at least three months to a short course of bilateral ECT followed by one-month's use of an antipsychotic without cardiovascular or cognitive deterioration.[7] On average, 16 patients with mild to severe dementia exhibited a clinically significant decrease in agitation.[7]

Duration of treatment effect and/or time to relapse

The effect of ECT was transient and lasted two weeks to seven months in patients who were treated for agitation and aggression.[11] In a group of four adults with dementia, the treatment effect lasted three to 12 months following two to four sessions of ECT.[7] Across 17 studies involving adults who were diagnosed with PD and comorbid depression, patients relapsed between one week and five years of being treated with ECT, where reported.[8]

Safety of electroconvulsive therapy for older adults with dementia

In the review involving 122 patients under treatment for agitation and aggression, six patients had delirium, two exhibited signs of postictal confusion and one had a seizure.[11] Treatment was postponed or terminated due to skin rash,[11] urinary tract infection,[11] and atrial fibrillation.[11] It was unclear whether events such as spontaneous seizures and confusion could be attributed to treatment or the prevailing condition of the patient.[11] Six out of 17 studies did not report on side effects.[11] Out of 116 patients with PD and comorbid depression, 31 (26.7%) exhibited signs of delirium, 10 (8.6%) had transient confusion, eight out of 27 were disoriented (not all were diagnosed with PD),[8] and one each exhibited agitation or stuttering or slurred speech.[8] Transient confusion and delirium resulted in termination or postponement of treatment.[8] One patient each experienced premature ventricular contraction and myocardial infarction or death. A third review reported that in one retrospective chart review series, out of 31 hospitalized patients with dementia, 15 exhibited signs of delirium within three days of starting treatment and one each had a prolonged seizure, transient ischemic attack, ventricular tachycardia, or atrial fibrillation.[7] none of the prospective studies that were included in this review reported on side effects or adverse events.[7] The fourth review reported that signs of short-term autonomic dysfunction were observed in an unspecified number of patients.[9]

Guidelines

No relevant evidence-based guidelines regarding the use of ECT for patients with dementia were found; therefore, no summary can be provided.

Limitations

A major limitation of the body of evidence on clinical effectiveness and safety of ECT for older adults with dementia is the low quality of the primary evidence. The primary studies

that were included in the systematic reviews were mainly case reports, case series and retrospective chart reviews that enrolled fewer than 30 patients. Despite being appropriate for studying chronic conditions with severe, variable, and transient symptoms, case reports and case series are inherently susceptible to selection, detection, and reporting biases.[10] Therefore, generalizable inferences on the effectiveness of ECT in the general population cannot be made from this report.[10]

A second major limitation of the body of evidence was that there was considerable variation in the characteristics of the primary studies, making narrative synthesis challenging. Across the systematic reviews there was heterogeneity in the patient populations, the components of the intervention, and the outcomes. Two reviews covered patients with LBD and/or DLB,[9,10] one reported on adults being treated for agitation and aggression,[11] one included adults diagnosed with PD and comorbid depression,[8] and the fifth covered older adults with or without depression.[7] ECT was administered concurrently with medication or other non-medication based interventions.[10,11] There was considerable heterogeneity in the ECT stimulus dose and pulse width, the number of sessions, the duration of single sessions, and the length of treatment across the studies that provided details.[7,8,11] Although all of the reviews reported on changes in outcomes of interest from baseline, there was variation in the types of depressive and psychotic outcomes discussed and the use (or lack thereof) of measurement scales.[7-11] The reviews also spanned an extensive timeframe incorporating information from primary studies that were published in 1975 through to 2017.[7-11] The technology has changed in that time period;[4] as such the attendant safety standards have likely changed.

Thirdly, by restricting this report to patients with dementia, this study is further limited in its coverage of ECT. Studies on ECT that focused on shared symptoms such as depression or cognitive loss rather than the specific clinical condition of dementia may have been excluded from the literature.

Finally, clinical evidence specific to insomnia, anxiety, psychomotor agitation, short-term memory loss,[8] and relevant evidence-based guidelines were not found in the literature.

Conclusions and Implications for Decision or Policy Making

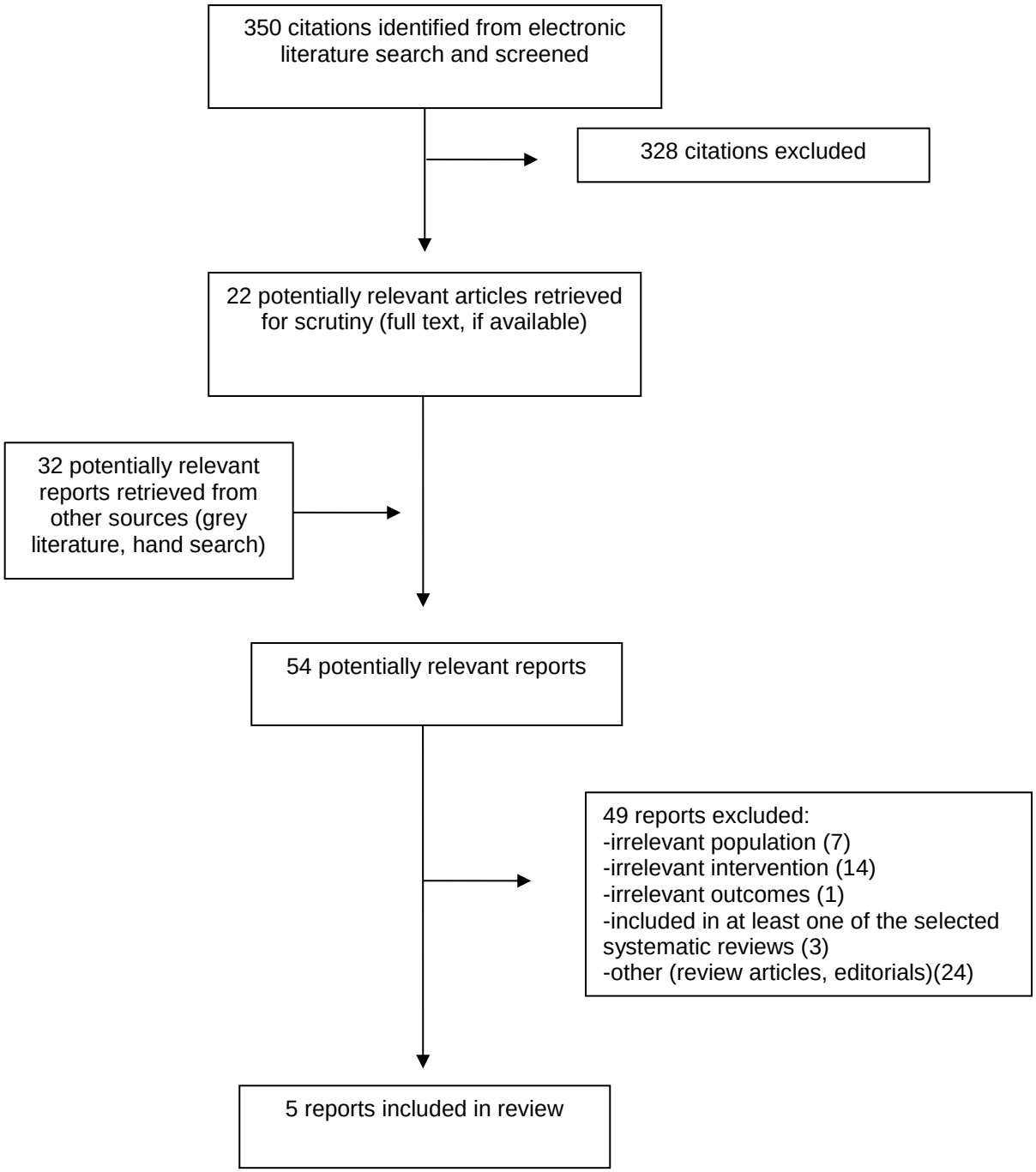
Five relevant systematic reviews[7-11] were identified that reported on primary studies that were published over an extensive period spanning 1975 through 2017; yet, no clear patterns emerged regarding the impact of ECT on the symptoms of dementia. While evidence derived primarily from case series and case reports suggested that ECT led to improvements in symptoms of depression[7-10] and problem behaviours,[7,9-11] some patients exhibited symptoms of confusion and other forms of cognitive decline.[7-9] In addition to the evidence being mixed and of low quality, some changes in clinical symptoms were reportedly transient.[7,8,11] Reports of safety issues ranged from delirium, seizures, stuttering and slurred speech to serious cardiovascular events, although it was not clear whether all of these incidents could be attributed to treatment or the prevailing condition of the patients.[7-9,11] No relevant evidence-based guidelines were found that addressed the use of ECT for the treatment of behavioural and psychological symptoms of dementia in older adults.

Caution must be taken in interpreting the evidence on clinical effectiveness and safety due to the sparsity of available literature and the low quality of the primary studies that were included in the systematic reviews. While the systematic reviews had some noteworthy strengths, there were serious limitations related to the quality and types of the primary studies, heterogeneity in the patient populations, variability of the components of the intervention, and differences in the reporting of outcomes. These limitations introduce a level of uncertainty in the findings and preclude generalizablity of the evidence to the Canadian context. While contemplating the lack of robust findings in the literature, decision and policy makers need to consider training requirements for providers, other quality controls for treatment protocols, the financial impact, and ethical issues relevant to ECT. Further research involving prospective study designs may help to produce evidence that will be useful in informing relevant public health policies.

References

1. Bouchard RW. Diagnostic Criteria of Dementia. *Can J Neurol Sci.* 2007;34(Supplement 1):S11-S18.
2. Government of Canada. Dementia. 2019; https://www.canada.ca/en/public-health/services/diseases/dementia.html, Accessed 2019 May 22.
3. Kerner N, Prudic J. Current electroconvulsive therapy practice and research in the geriatric population. *Neuropsychiatry (London).* 2014;4(1):33-54.
4. Enns MW, Reiss J, Chan P. Electroconvulsive therapy - position paper. Ottawa (ON): Canadian Psychiatric Association; 2010: https://www.cpa-apc.org/wp-content/uploads/ECT-CPA_position_paper_27-revision_1-web-EN.pdf. Accessed 2019 May 22.
5. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008. http://www.bmj.com/content/bmj/358/bmj.j4008.full.pdf. Accessed 2019 May 22.
6. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.
7. Liu AY, Rajji TK, Blumberger DM, Daskalakis ZJ, Mulsant BH. Brain stimulation in the treatment of late-life severe mental illness other than unipolar nonpsychotic depression. *Am J Geriatr Psychiatry.* 2014;22(3):216-240.
8. Borisovskaya A, Bryson WC, Buchholz J, Samii A, Borson S. Electroconvulsive therapy for depression in Parkinson's disease: systematic review of evidence and recommendations. *Neurodegener Dis Manag.* 2016;6(2):161-176.
9. Connors MH, Quinto L, McKeith I, et al. Non-pharmacological interventions for Lewy body dementia: a systematic review. *Psychol Med,.* 2018 Aug;48(11):1749-1758.
10. Morrin H, Fang T, Servant D, Aarsland D, Rajkumar AP. Systematic review of the efficacy of non-pharmacological interventions in people with Lewy body dementia. *Int Psychogeriatr.* 2018;30(3):395-407.
11. van den Berg JF, Kruithof HC, Kok RM, Verwijk E, Spaans HP. Electroconvulsive therapy for agitation and aggression in dementia: a systematic review. *Am J Geriatr Psychiatry.* 2018;26(4):419-434.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Morrin, 2018[10] United Kingdom	A systematic review of the efficacy of all reported nonpharmacological interventions for cognitive and non-cognitive symptoms of LBD 15 studies published between 1995 and 2017 were included in the systematic review One uncontrolled study published in 2009 and one case series published in 2003 met the inclusion criteria for this report	15 adults with LBD (n=7) or DLB (n=8) Mean age: 70.3 years (95% confidence interval, 64.8 to 75.8)	Intervention: ECT Comparator(s): None	Changes in depressive symptoms (HDRS score); changes in psychotic symptoms Follow-up: Not specified Outcomes involving other technologies or younger patients were not included in this review
van den Berg, 2018[11] The Netherlands	A systematic review to summarize the scientific literature describing the efficacy and safety of ECT for the treatment of agitation and aggression in dementia; All 17 studies published between 1991 and March 10, 2017 met the inclusion criteria for this report: one before-and-after cohort study and one case control study were prospective while five chart reviews, case series, and case reports each were retrospective	122 adults with dementia being treated for agitation and aggression Gender: 28 male, 91 female, and 3 unspecified Age range: 54 to 98 years Excluded: patients with HD, PD without dementia, and traumatic brain injury, and patients primarily treated with ECT for depression, mania, or bipolar disorder.	Intervention: ECT Comparator(s): None	Changes in problem behaviour; treatment response rate; number of patients with severe side effects or adverse events Follow-up: Not specified The number of patients referred for additional ECT with or without maintenance ECT and the range of symptom-free follow-up periods were reported but not included in this review
Connors, 2017[9] Australia and United Kingdom	A systematic review of non-pharmacological interventions for patients with LBD Two RCTs, seven case series and twelve case studies published	22 patients with DLB Age: NR[b]	Intervention: ECT Comparator(s): None	Primary outcomes: Changes in depressive and psychiatric/ psychotic symptoms; changes in cognition Secondary Incidence of side effects

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	between 2002 and October 30, 2016 were included in the systematic review Three case series and one case report published between 2002 and 2016 met the inclusion criteria for this report[a]			Follow-up: Not specified Outcomes regarding perceived acceptability and dropout rates were not included in this report
Borisovskaya, 2016[8] United States	A summary of the literature on the use of ECT to treat depression in patients with PD All forty-three included studies published between 1975 and September 2015 met the inclusion criteria for this report: one retrospective case control study, two chart reviews, 13 case series, and 27 case reports	116 adults diagnosed with PD and comorbid depression[c] Age range: 52 to 83 years (plus one patient aged 33 years)	Intervention: ECT Comparator(s): None	Changes in depressive symptoms; changes in cognition; changes in motor function; treatment response rate; duration of treatment effect; incidence of side effects Follow-up: Not specified
Liu 2014,[7] Canada	A systematic review of evidence relevant to the use of brain stimulation interventions in older adults (i.e., aged ≥65 years) for the treatment of severe mental illness Forty-three studies published between 1991 and March 7, 2012 were included in the systematic review Thirteen studies that were published between 1991 and 2001 met the inclusion criteria for this report: three prospective before-and-after studies, three retrospective chart	146 adults with dementia with or without depression Mean age: ≥65 years (range, 51 to 97; not reported) Excluded: studies that did not use brain stimulation, used brain stimulation only as an investigational rather than a treatment tool, or reported only on unipolar depression or on a neurological disorder without a co-morbid psychiatric illness	Intervention: ECT Comparator(s): None	Changes in cognition or mood; treatment response, incidence of side effects and adverse events Follow-up: Not specified

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	reviews, four case series, and three case reports			

DBL = dementia with Lewy Bodies; ECT = electroconvulsive therapy; HD = Huntington disease; LBD = Lewy body dementia; PD = Parkinson disease; RCT = randomized controlled trial

[a] One of the case series did not include a full text article

[b] Two of the included studies enrolled patients with mean ages 73.6±10.6 and 71.6±7.3 as reported by Morrin et al., (2018)

[c] One patient diagnosed with bipolar mania did not exhibit signs of depression

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Systematic Reviews using AMSTAR 2[5]

Strengths	Limitations
Morrin, 2018[10]	
• The statement of objectives included the population, interventions, and outcomes of interest • The authors searched six databases, and provided key words and a search strategy • The study eligibility criteria included the population and intervention • The authors provided a detailed description of the study exclusion process • The authors described the populations in detail as provided by the included studies • An explicit statement that the review methods were established prior to the conduct of the review was provided • The quality of included studies was assessed with the CARE criteria checklist and the Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies • Levels of evidence on outcomes were evaluated using guidelines from the Oxford center for Evidence-Based Medicine • Four of five authors declared that they had no conflicts of interest	• The authors did not report duplicate study selection and data extraction • The study eligibility criteria did not include study types and outcomes of interest, as such, the authors did not provide an explanation for their inclusion of specific study designs • The authors did not describe the parameters of the intervention • The authors did not provide a list of excluded studies nor justification for the exclusion criteria • The authors did not provide adequate descriptions of the study settings • A timeframe for follow-up was not clearly specified • The sources of funding of the primary studies were not included • One author had received financial support from multiple manufacturing companies
van den Berg, 2018[11]	
• The statement of objectives included the population, intervention, and outcomes of interest • The authors searched three databases, and provided key words and a search strategy • The authors performed study selection and data extraction in duplicate • The study eligibility criteria included the population, intervention, study types, and outcomes of interest • The authors described the populations and parameters of the intervention in detail as provided by the included studies • The authors declared that they had no conflicts of interest	• An explicit statement that the review methods were established prior to the conduct of the review was not provided • The authors did not provide an explanation for their inclusion of specific study designs • The authors did not provide a list of excluded studies nor justification for the exclusion criteria • The authors did not provide adequate descriptions of the study settings • The authors did not critically assess the quality of the evidence • A timeframe for follow-up was not clearly specified • The sources of funding of the primary studies were not included
Connors, 2017[9]	
• The statement of objectives included the population and interventions • The authors searched 14 databases, and provided key words and a search strategy • The authors performed study selection and data extraction in duplicate • The study eligibility criteria included the population, intervention	• The statement of objectives did not include the outcomes of interest • The study eligibility criteria did not indicate study types or outcomes of interest • The parameters of the intervention were not described • The authors did not provide an explanation for their inclusion of specific study designs • The authors did not provide a list of excluded studies nor

Table 3: Strengths and Limitations of Systematic Reviews using AMSTAR 2[5]

Strengths	Limitations
• The authors described the populations in detail as provided by the included studies • An explicit statement that the review methods were established prior to the conduct of the review was provided • The authors assessed the quality and risk of bias of the included studies with the Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies and the NICE Methodology Checklist for Qualitative Studies • Six out of nine authors declared that they had no conflicts of interest	justification for the exclusion criteria • The authors did not provide adequate descriptions of the study settings • The authors did not critically assess the quality of the body of evidence for each outcome • A timeframe for follow-up was not clearly specified • The sources of funding of the primary studies were not included • Three authors had received compensation from manufacturing companies
Borisovskaya, 2016[8]	
• The statement of objectives included the population, intervention, and outcomes of interest • The authors searched four databases, provided key words and a search strategy, and did not include language restrictions • The authors performed study selection and data extraction in duplicate • The study eligibility criteria included the population, intervention, study types, and outcomes of interest • The authors described the populations and parameters of the intervention in detail • The authors discussed limitations of the review driven by heterogeneity of included studies and the potential of reporting bias in case series and reports • The authors declared that they had no conflicts of interest	• An explicit statement that the review methods were established prior to the conduct of the review was not provided • The authors did not provide an explanation for their inclusion of specific study designs • The authors did not provide a list of excluded studies nor justification for the exclusion criteria • The authors did not provide adequate descriptions of the study settings • Primary studies that had reporting gaps were included • The authors did not critically assess the quality of the included studies nor the overall quality of the evidence for each outcome • A timeframe for follow-up was not clearly specified • The sources of funding of the primary studies were not included
Liu, 2014[7]	
• The statement of objectives included the populations and interventions • The authors searched three databases, and provided key words and a search strategy • The study eligibility criteria included the population and intervention • The authors discussed limitations of the review such as the small size of the studies and the types of studies	• The statement of objectives did not include the outcomes of interest • The authors did not report duplicate study selection and data extraction • The study eligibility criteria did not include study types or outcomes of interest • The authors did not describe the populations and parameters of the interventions in detail • The authors did not assess the quality of the included studies nor the overall quality of evidence for each outcome • An explicit statement that the review methods were established prior to the conduct of the review was not provided • The authors did not provide an explanation for their inclusion of specific study designs • The authors did not provide a list of excluded studies nor justification for the exclusion criteria • The authors did not provide adequate descriptions of the study settings • A timeframe for follow-up was not clearly specified • The sources of funding of the primary studies were not

Table 3: Strengths and Limitations of Systematic Reviews using AMSTAR 2[5]

Strengths	Limitations
	included • Three of five authors received funding from manufacturing companies although they indicate that the support did not represent conflicts of interest

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings Included Systematic Reviews

Main Study Findings	Authors' Conclusion
Morrin, 2018[10]	
Changes in depressive symptoms • Mean HDRS score (n=8): 23 point reduction from 38.0±5.8 before ECT to 15.0±9.6 (P < 0.005); indicating statistically significant clinical improvement[a] • MMSE changed from a mean of 24 points to a range of 23 to 28 points in one patient, from 19 points to 23 points in a second patient, and from 28 points to 21 points in a third patient. The MMSE remained the same in the fourth patient. The change was not reported in the remaining three patients • Symptoms of depression improved in two patients albeit temporarily in one **Changes in psychotic symptoms** • Visual hallucinations decreased in intensity in two patients but recurred in one out of seven patients • Delusion was temporarily reduced in one patient	*"Though there has not been any study suggesting hastening of cognitive decline by ECT in LBD, there is a need for studies investigating long-term cognitive effects of ECT in people with LBD."* (p403)
van den Berg, 2018[11]	
Outcome measurements were reported primarily prior to the fifth ECT session. **Treatment response rate** • Proportion of patients who responded to treatment: 87.7% (107/122) achieved substantial clinical improvement prior to 5th session **Changes in problem behaviour** • Improvements included less agitation and aggressive behaviour, cessation of yelling or screaming, and return to eating **Duration of treatment effect** • Time to relapse: 2 weeks to 7 months • Proportion referred for maintenance ECT: 62% (51/82) • Some patients required psychotropic medication while	"*The reviewed articles suggest that ECT could be an effective treatment for treatment-resistant agitation and aggression in dementia, with few adverse consequences. Because of the substantial risk of selection bias, the designs of the reviewed studies, their small number, and their small numbers of patients, this review does not allow us to draw solid conclusions about the safety and effectiveness of ECT for agitation and aggression in dementia.*" (p433)

Table 4: Summary of Findings Included Systematic Reviews

Main Study Findings	Authors' Conclusion
others did not require long-term medication • Twenty-five out of 107 patients were lost to follow-up **Severe side effects and adverse events** • Side effects (n=122): delirium (n=6), seizure (n=1), severe postictal confusion (n=2) • Adverse events leading to postponement or termination of treatment: delirium and skin rash (n=1), delirium secondary to urinary tract infection (n=1), atrial fibrillation (n=1) • Adverse events with unclear origin: spontaneous seizures, confusion The number of patients referred for additional ECT with or without maintenance ECT and the range of symptom-free follow-up periods were not included in this report	
Connors, 2017[9]	
Changes in depressive and psychiatric/psychotic symptoms/problem behaviours One patient demonstrated less depression and fewer neuropsychiatric symptoms up to two weeks following treatment. Seven patients experienced less depression; two had fewer hallucinations Six patients reported less depressive and psychotic symptoms (abstract only) **Changes in cognition** Two out of seven patients exhibited confusion immediately after ECT **Side effects and adverse events** An unspecified number of patients displayed signs of short-term autonomic dysfunction. No other adverse events were reported. Outcomes such as perceived acceptability and drop-out rates were not included in this report	"*Overall, given the heterogeneity of interventions, small sample sizes, and poor quality of research, no treatment recommendations can be offered."(*p8)
Borisovskaya, 2016[8]	
Changes in depressive symptoms Proportion of patients with improvement: 93.1% (108/116) **Changes in cognition** Proportion of patients with improvement, no change, worse cognition, not reported, incomplete treatment (n=117):[b] 2.6% (3), 23.9% (28), 1.7% (2), 64.1% (75), 1.7% (2), respectively **Duration of treatment effect** Time to relapse (n=17 studies): 1 week to 5 years **Side effects and adverse events** • Delirium (n=31), transient confusion (n=10), stuttering and slurred speech (n=1), agitation (n=1), disorientation (n=8 out	"*ECT is a beneficial treatment for patients suffering from PD and depression, often effective for mood and motor symptoms. Common side effects include delirium, transient confusion, falls, urinary retention and rarely exacerbation of abnormal movements and motor symptoms. Cognitive losses are not universal during a course of ECT*."(p173)

Table 4: Summary of Findings Included Systematic Reviews

Main Study Findings	Authors' Conclusion
of 27), premature ventricular contraction (n=1), myocardial infarction or death (n=1) • Side effects leading to postponement or termination of treatment: delirium and transient confusion Impact on motor function was not included in this report	
Liu, 2014[7]	
Changes in depressive symptoms • Mean MADRS score (n=31): 12.3 point reduction, suggesting clinical improvement • Mean MMSE score: No significant change @ six months but declined after six ECT sessions (n=12); 1.62 point increase (n=31), suggesting clinical improvement **Changes in cognition and/or mood** • Incidence of confusion (n=40): temporary increase in confusion 32.5%, suggesting temporary clinical decline • Cognitive decline (n=12): Eight patients assessed six weeks after the last ECT session; the decline persisted in four patients for six months after the last ECT session **Changes in problem behaviour** • On average, 16 patients with mild to severe dementia exhibited a clinically significant decrease in agitation; one patient did not improve **Duration of treatment effects** Time to relapse (n=4): 3 to 12 months following two to four sessions **Side effects and adverse events** • Out of 31 patients: 15 with delirium within three days of treatment , one each with transient ischemic attack, prolonged seizure, atrial fibrillation, and one episode of ventricular tachycardia	"*…patients suffering from depression in the context of dementia seem to experience relief from depression in response to ECT. However, some of them experience prominent confusion and delirium especially with bi-temporal ECT*" (p5) "*ECT, particularly bilateral ECT, seems to be effective in the treatment of behavioral and psychological symptoms associated with dementia. The concern of worsening cognitive impairment is not substantiated by the current literature, notwithstanding the limitations of this literature. However, given the potentially serious adverse effects associated with psychotropic medications in this population, larger studies of ECT … are warranted."* (p7)

ECT = electroconvulsive therapy; HDRS = Hamilton Depression Rating Scale; LBD = Lewy Bodies dementia; MADRS = Montgomery-Asperg Depression Rating Scale; NR = not reported

[a] Included in Liu et al.(2014) and Connors et al.(2017)

[b] Published table included 117 instead of 116 patients (p 167) in Borisovskaya et al. (2016)

Appendix 5: Overlap between Included Systematic Reviews

Table 5: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation				
	Morrin, 2018[10]	van den Berg, 2018[11]	Connors, 2017[9]	Borisovskaya, 2016[8]	Liu 2014,[7]
Fazzari et al., 2015	-	X	-	-	X
Ujkaj et al., 2012		X	-	-	X
Takahashi *et al.,* 2009	X	-	X	-	X
Rasmussen *et al.,* 2003	X	-	X	-	X
Grant and Mohan, 2001	-	X	-	-	X

Primary studies that were covered by single reviews are not included in this table

Appendix 6: Additional References of Potential Interest

Evidence-based guidelines published prior to 2014

National Institute for Health and Care Excellence. Guidance on the use of electroconvulsive therapy. United Kingdom: National Institute for Health and Care Excellence; 2003: https://www.nice.org.uk/guidance/ta59/resources/guidance-on-the-use-of-electroconvulsive-therapy-pdf-2294645984197 Accessed 2019 May 22.

Donnelly M, Eyre J, Goldner E, Gray J, Kane B. Electroconvulsive therapy guidelines for health authorities in British Columbia. Vancouver (BC): Mental Health Evaluation & Community Consultation Unit; British Columbia Ministry of Health Services; 2002: http://www.health.gov.bc.ca/library/publications/year/2002/MHA_ect_guidelines.pdf Accessed 2019 May 22.

Richard J. The Practice of electroconvulsive therapy: recommendations for treatment, training, and privileging: a task force report of the American Psychiatric Association. 2002;159(2).

Guideline on ECT that did not focus on dementia

Enns MW, Reiss J, Chan P. Electroconvulsive Therapy - Position Paper. Canadian Psychiatric Association; 2010.

Guidelines without evidence of a systematic literature search

Shaji KS, Sivakumar PT, Rao GP, Paul N. Clinical practice guidelines for management of dementia. Indian J Psychiatry. 2018;60(Suppl 3):S312–S328.

Demas M. Provincial clinical knowledge topic: electroconvulsive therapy, adult – inpatient, ambulatory, v1.0. Edmonton (AB): Alberta Health Services; 2017: https://extranet.ahsnet.ca/teams/policydocuments/1/klink/et-klink-ckv-electroconvulsive-therapy-adult-inpatient-ambulatory.pdf Accessed 2019 May 22.

Tible OP, Riese F, Savaskan E, von Gunten A. Best practice in the management of behavioural and psychological symptoms of dementia. Ther Adv Neurol Disord. 2017; 10(8):297-309.

Ministry of Health Social Services and Equality. Clinical practice guideline on the management of depression in adults. Galician Agency for Health Technology Assessment; 2014: http://www.guiasalud.es/contenidos/GPC/GPC_534_Depresion_Adulto_Avaliat_compl_en.pdf Accessed 2019 May 22.

California Workgroup on Guidelines for Alzheimer's Disease Management. Guideline for Alzheimer's disease management; 2008: https://www.alzheimersla.org//wp-content/uploads/2016/01/Professionals-Guideline-FullReport-CA.pdf Accessed 2019 May 22.