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Response rate and subjective memory after electroconvulsive therapy in depressive disorders with psychiatric comorbidity

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ABSTRACT

Background: Response rates after and tolerability of electroconvulsive therapy (ECT) in depressive disorders with psychiatric comorbidity are uncertain.
Methods: Data on patients with a depressive episode and a first course of ECT were collected from the Swedish National Quality Register for ECT. Logistic regression analyses, adjusted for gender, age, and depressive episode severity, were used to compare patients with and without comorbidity. The clinical response assessment Clinical Global Impression - Improvement Scale was used in 4413 patients and the memory item from the Comprehensive Psychiatric Rating Scale was used for subjective memory impairment rating after ECT in 3497 patients.
Results: In patients with depressive disorder and comorbid personality disorder or anxiety disorder, 62.7% and 73.5%, respectively, responded after ECT compared with 84.9% in patients without comorbidity [adjusted odds ratio (aOR) 0.43, 95% confidence interval (CI) 0.34–0.55, and aOR 0.61, 95% CI 0.51–0.73, respectively]. The proportion of responding patients with comorbid alcohol use disorder was 77.1%, which was not significantly different from that in patients without comorbidity (aOR 0.75, 95% CI 0.57–1.01). The impact of comorbidity decreased with higher age and depressive episode severity. Subjective ratings of memory impairment did not differ between patients with and without comorbidity.
Limitations: Observational non-validated clinical data.
Conclusions: The response rate after ECT in depression may be lower with concurrent personality disorder and anxiety disorder; however, the majority still respond to ECT. This implies that psychiatric comorbidity should not exclude patients from ECT.

1. Introduction

Comorbid psychiatric disorders are highly prevalent in depression, with estimated prevalence rates just over 40% for personality disorder and over 20% for alcohol use disorder (Hasin et al., 2018; Melartin et al., 2002). Prevalence of comorbid anxiety disorder varies between 36% and 57% in studies (Hasin et al., 2018; Kimura et al., 2020; Melartin et al., 2002). Comorbidity increases the risks of suicide attempts and treatment resistance, and lowers the likelihood of remission of the depressive episode (Bolton et al., 2010; Howland et al., 2009; Tyrer et al., 2015). Psychiatric comorbidities call for consideration in the treatment strategy regarding which disorders to prioritise and how the comorbid disorders could affect each other and the respective treatments (NICE, 2010).

Antidepressant medication is a first-choice treatment in major depressive episodes (NICE, 2010), but only a minority of the patients remit with the first antidepressant drug treatment (Rush et al., 2006). Electroconvulsive therapy (ECT) is also a well-established treatment for affective disorders, and in most guidelines considered first-line treatment for severe depressive episodes that are life-threatening or where a rapid response is required. It is a highly effective treatment for depression, with response rates often above 70% (Kellner et al., 2020). ECT seems to be more effective in older patients, in more severe depressive episodes, and in depression with psychotic symptoms (van Diermen et al., 2018). Shorter episode duration also predicts a higher response rate (Haq et al., 2015). Still, the antidepressant effect varies and there is a need for additional predictors of whether an individual patient will

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benefit from the treatment.

In the clinical setting, ECT is often suspected to be less effective and associated with more subjective cognitive side effects in some patient groups, such as depressed patients with psychiatric comorbidities, but the scientific support for this is scarce. Studies of patients with depression and concurrent personality disorder are few, but have mainly shown less effect of ECT compared with in patients without personality disorder (de Vreede et al., 2005; Nordenskjöld et al., 2012; Prudic et al., 2004). One study looking specifically at borderline personality disorder found weaker response in the borderline group, but not in other personality disorders (Feske, 2004). A recent study found no significant differences in ECT response when comparing patients with high and low scores on a screening instrument for borderline personality disorder (Lee et al., 2019).

Anxiety disorder and alcohol use disorder have been investigated even less. One study found that the short-term response rate after ECT did not differ in depressive disorders with or without comorbid anxiety disorders and substance use disorders (Nordenskjöld et al., 2012). A later study found that comorbid anxiety diagnoses or substance use disorders had lower remission rates of depression after ECT (Brus et al., 2017a). In contrast, another study found that a history of alcohol use disorder was associated with a higher antidepressant response rate after ECT (Aksay et al., 2017). There was no significant difference in response rates after ECT between patients with major depressive episodes alone and patients with major depressive disorder and posttraumatic stress syndrome (Kaster et al., 2018). Thus, the few available studies are contradictory.

Cognitive side effects of ECT include transient impairments in anterograde functions such as executive functions, visuospatial memory, and attention, as well as retrograde amnesia (Meeter et al., 2011; Semkovska et al., 2011). A range of both objective and subjective measures have been used to investigate cognitive functions after ECT. These were not all optimised for post-ECT effects and generated incongruous results, leaving uncertainty as to the extent and duration of memory impairment after ECT (Fernie et al., 2014; Jelovac et al., 2016; Semkovska and McLoughlin, 2013; Vasavada et al., 2017). Evaluating the impact of ECT on cognition is complicated by the fact that several psychiatric disorders, including depression, anxiety and personality disorders, and alcohol use disorders, have negative impacts on cognitive function (Ahern and Semkovska, 2017; Crowe et al., 2020; Maurex et al., 2010; Moran, 2016; Rock et al., 2014). Further, the relation between cognitive side effects of ECT and psychiatric comorbidities is largely unknown, with one study failing to detect any increased risk of subjective memory impairment in patients with personality disorders (Brus et al., 2017b).

There are other neurostimulation techniques that might offer an alternative to ECT for management of depressive episodes, such as repetitive transcranial magnetic stimulation (rTMS). In general, rTMS is less effective than ECT, but the cognitive side effects are more favourable and there might be differences in effectiveness between patient subgroups (Ren et al., 2014). The impact of psychiatric comorbidity on the effectiveness of rTMS is not yet extensively examined, but one study found that the effect of rTMS on depression seemed to be the same regardless of concurrent comorbid anxiety disorder (Clarke et al., 2019). With alternative treatments available, information on the outcomes of ECT in depression with psychiatric comorbidities would be of relevance.

This study aimed to investigate response rates and subjective memory impairment after ECT for depressive episodes in patients with concurrent personality disorder, anxiety disorder, or alcohol use disorder, and how outcomes were modified by age and depressive episode severity. Our hypothesis was that patients with comorbidities would have lower response rates and more subjective memory impairment compared with patients without comorbidities. We also hypothesised that the influence of comorbidity on outcome would decrease with increasing depressive episode severity.

2. Methods

This was a cross-sectional study based on data from the Swedish National Quality Register for ECT (SNQR-ECT) combined with data from two registers maintained by the Swedish National Board of Health and Welfare: the National Patient Register and the Cause of Death Register. Register linkage was performed using the unique personal identification number, a national registration number that each Swedish resident is assigned at birth or immigration.

Since 2011, all Swedish hospitals offering ECT have reported data to the SNQR-ECT. All patients receiving ECT in Sweden are included in the register if they do not actively decline participation; coverage has increased from 76% in 2012 to 90% in 2017. The register encompasses details from each course of treatment, including personal identification number, indication for treatment, diagnoses, and technical treatment data. In all cases, ECT was administered using a brief bidirectional, constant current pulse with either MECTA (MECTA Corp, Tualatin, OR, USA) or Thymatron (Somatics LLC., Venice, FL, USA) devices. An attending psychiatrist determined the number of sessions and electrode placements.

Since 1997, inpatient discharge diagnoses based on the International Classification of Disease 10th version (ICD-10) have been recorded in the National Patient Register, with complete national coverage. Information on date of discharge, length of stay, main diagnosis, and up to seven additional diagnoses codes are available for each admission. The National Patient Register also includes medical procedures (such as ECT), department and hospital, as well as personal identification number. Since 2001, information from outpatient visits to hospital-connected specialist care is included. The Cause of Death Register contains information on all deaths of Swedish residents since 1960, based on death certificates.

2.1. Sample definition

Inclusion criteria were ECT given as an index course (ECT two or three times a week), a diagnosis of a moderate or severe depressive episode in bipolar affective disorder, first depressive episode, or recurrent depressive disorder (ICD-10 codes F31.3–F31.5, F32.1–F32.3, F33.1–F33.3) in either the SNQR-ECT or the National Patient Register when receiving ECT, and age of 18 years or older. It may be assumed that a patient is more likely to receive another course of ECT if the first one is successful. To avoid bias, only patients without earlier registration of ECT in the National Patient Register were included and if a patient had received more than one index course of ECT during the timeframe for inclusion, only the first course was included. Exclusion criteria were fewer than six ECT sessions in the index course and ICD-10 diagnosis of schizophrenia or schizoaffective disorder (F20 or F25). To ensure that the patients had received a course of treatment long enough to achieve a probable antidepressant effect, a lower limit of six ECT sessions was chosen, as previous literature suggests that a majority of patients have achieved a sustained response at that point (Husain et al., 2004). This resulted in a sample of 4890 patients (Fig. 1), among whom patients with available outcome measures were selected.

2.2. Outcome measures

The outcomes of interest were response and subjective memory impairment. To assess response to ECT, the Clinical Global Impression - Improvement Scale (CGI-I) was used; a scale where an investigator rates a patient's improvement based on the investigator's view of the patient's symptoms and functioning in relation to their experience of the particular patient population (Guy et al., 1976). The psychiatrist responsible for the patient's care evaluates the treatment using CGI-I within a week after the patient's last ECT session. CGI-I is rated between 1 (very much improved since initiation of treatment) to 7 (very much worse since initiation of treatment). CGI-I scores of 1 or 2 correspond to a reduction

of 50% or more on the Hamilton Rating Scale for Depression (HRSD), which is an established response criterion (Leucht et al., 2013).

The memory item from the Comprehensive Psychopathological Rating Scale (CPRS-M) was used to assess subjective memory impairment (Asberg et al., 1978). CPRS-M reflects the present disturbance of memory recall compared with previous ability according to the patient. CPRS-M is rated on a 7-point scale and specified as 0 = memory as usual, 2 = occasional increased lapses of memory, 4 = reports of socially inconvenient or disturbing loss of memory, and 6 = complaints of complete inability to remember. The patients rated a CPRS-M score immediately before and after the treatment series. Memory impairment was defined as present if the score had risen by $\geq$ 2 points after ECT (Brus et al., 2017b).

2.3. Potential predictors

The variables examined as potential predictors were the following comorbidity diagnoses, identified through ICD-10 codes in the National Patient Register: personality disorder (F60) during lifetime, anxiety disorder (F40.0, F40.1, F41.0, F41.1, F42–F44) during the past year, and alcohol use disorder (F10) during the past year.

2.4. Statistical methods

Descriptive data including gender, age, depressive episode severity, and ECT parameters were tabulated. For continuous variables found to have a normal distribution, means and standard deviation were presented, whereas medians and interquartile ranges were used for ordinal variables and non-normally distributed continuous variables. Differences in the outcomes in patients with the comorbidity of interest, compared with those without comorbidity, were first analysed with univariate logistic regression.

Age and depressive episode severity were considered potential confounders (van Diermen et al., 2018). Depressive episodes were classified in the following hierarchy: I) moderate, II) severe without psychotic features, or III) severe with psychotic features, based on the diagnosis with highest severity classification from SNQR-ECT or National Patient Register at the time of ECT. As there might be a non-linear relationship between age and outcome, age was categorised into clinically relevant categories in line with previous similar studies (Brus et al., 2017a; Heijnen et al., 2019). Gender was not considered a potential confounder for response, as it has not previously been identified to be associated with ECT outcome (Brus et al., 2017a). Regarding cognitive side effects, there is a possible difference due to gender, which was therefore included in the adjusted models for memory impairment (Sackeim et al., 2007). Adjusted models were performed with the variables assumed to be confounders added simultaneously into multivariate logistic regressions. To examine the effect of multiple comorbidities, the two other comorbidity diagnoses were added into the adjusted analyses as a control step, to see if they had any substantial effect on the odds ratios. All analyses were performed in R 3.6.2 (R Core Team, 2019).

2.5. Ethics

The study was approved by the Ethical Review Board in Uppsala, Sweden (registration number 2016/442).

3. Results

3.1. Demographic characteristics

In the total sample of 4890 patients, 512 (10.5%) of the patients had personality disorder, 1216 (24.9%) had anxiety disorder, and 349 (7.1%) had alcohol use disorder. The groups were overlapping, so that 1397 (28.6%) patients in the sample had one comorbidity diagnosis, 301 (6.2%) had two, and 26 (0.5%) had all three. Borderline personality disorder constituted 48.8% of the personality disorder group. The comorbidity groups differed from the non-comorbidity group in several aspects (Table 1). There was a narrow majority of females among patients without comorbidity. Both the personality disorder and anxiety disorder groups comprised more females than the non-comorbidity group, whereas there was a majority of males in the alcohol use disorder group. Median age was lower in all comorbidity groups compared with the non-comorbidity group. All comorbidity groups had smaller proportions of severe depressive episodes with psychotic features and greater proportions of both severe depressive episodes without psychotic features and moderate episodes compared with the non-comorbidity group.

Of the 4890 patients, 4413 (90.2%) had CGI-I ratings. Patients without CGI-I assessments differed from patients with CGI-I assessments in their distribution of depressive episode severity, with more moderate and fewer severe episodes. Neither gender distribution nor median age differed between patients without and with CGI-I assessments. CPRS-M ratings were available in 3497 (71.5%) patients. Patients without CPRS-M assessments did not differ in distribution of depressive episode severity, gender distribution, or median age (data not shown).

3.2. Outcome

The proportions of patients who responded to ECT in the different groups are seen in Table 2. The odds ratios represent the likelihood of response for a patient with depression and the specific psychiatric comorbidity diagnosis compared with a patient with depression without comorbidity. Comorbid personality disorder was associated with a lower likelihood of response, and remained lower after adjusting for age and depressive episode severity [adjusted odds ratio (aOR) 0.43, 95% confidence interval (CI) 0.34–0.55] (Fig. 2). Similarly, patients with comorbid anxiety disorder were less likely to achieve response than the non-comorbidity group, and the likelihood for response was still significantly lower after adjusting for age and depressive episode severity (aOR 0.61, 95% CI 0.51–0.73). The unadjusted odds ratio indicated a lower likelihood of response in patients with alcohol use disorder than in patients without comorbidity, but the difference was no longer significant after adjusting for age and depressive episode severity (aOR 0.75, 95% CI 0.57–1.01).

When examining the variables in the adjusted analyses, both age and depressive episode severity had similar effects on the odds of response to ECT as the comorbidities themselves (Table 3). Controlling for the overlapping comorbidity groups by adjusting for multiple comorbidity diagnoses did not have any relevant effect on the odds ratios or the confidence intervals (data not shown).

The proportions of patients with subjective memory impairment in the different groups are seen in Table 2. Comorbid personality disorder and anxiety disorder were both associated with higher likelihood of subjective memory impairment in the unadjusted logistic regressions, but after adjusting for age, gender, and depressive episode severity, these groups no longer differed from the non-comorbidity patients (aOR 1.03, 95% CI 0.76–1.37 and aOR 1.20, 95% CI 0.97–1.47, respectively) (Fig. 2). The variables in the adjusted analyses can be seen in Table 4. Patients with alcohol use disorder did not have more subjective memory impairment than the non-comorbidity patients (OR 1.10, 95% CI 0.76–1.55).

3.3. Analysis of patients excluded due to short ECT course

When comparing patients who received fewer than six ECT sessions with patients with longer courses of ECT, we did not find any difference in the proportions of patients with anxiety disorder or alcohol use disorder (26.6% vs. 24.9%, $\chi^2(1) = 1.54$, $P = .22$; 6.8% vs. 7.1%, $\chi^2(1) = .18$, $P = .67$, respectively), but there was a greater proportion of patients with personality disorder (12.8% vs. 10.5%, χ^2 (1) = 5.25, $P = .02$). When comparing patients with personality disorder receiving fewer than

Table 1
Demographic, clinical characteristics, and technical treatment details of the comorbidity groups at assessment after electroconvulsive treatment, by outcome measures Clinical Global Impression – Improvement Scale (CGI-I) and the memory item from the Comprehensive Psychopathological Rating Scale.

	Total sample	No comorbidity		Personality disorder		Anxiety disorder		Alcohol use disorder	
		CGI-I	Subjective memory	CGI-I	Subjective memory	CGI-I	Subjective memory	CGI-I	Subjective memory
Number of patients	4 890	2 888	2 304	448	367	1 074	832	315	243
Females, n (%)	2 757 (56.4)	1 574 (54.5)	1 264 (54.9)	321 (71.7)	255 (69.5)	659 (61.4)	508 (61.1)	130 (41.3)	99 (40.7)
Median age, years (IQR)	52 (30)	56 (30)	56 (30)	40 (22)	38 (22)	45 (26)	45 (26)	49 (21)	49 (22)
Depression severity, n (%)	843 (17.2)	436 (15.1)	368 (16.0)	106 (23.7)	86 (23.4)	201 (18.7)	174 (20.9)	75 (23.8)	55 (22.6)
- Moderate	2 811 (57.5)	1 590 (55.1)	1 263 (54.8)	282 (62.9)	237 (64.6)	664 (61.8)	507 (60.9)	202 (64.1)	160 (65.8)
- Severe without psychosis	1 236 (25.3)	862 (29.8)	673 (29.2)	60 (13.4)	44 (12.0)	209 (19.5)	151 (18.1)	38 (12.1)	28 (11.5)
- Severe with psychosis									
Median seizure duration , s (IQR)	35 (18)	35 (19)	35 (19)	33 (16)	33 (18)	34 (18)	34 (17)	32 (23)	32 (24)
Median pulse width , ms (IQR)	0.5 (0.0)	0.5 (0.0)	0.5 (0.0)	0.5 (0.0)	0.5 (0.05)	0.5 (0.0)	0.5 (0.0)	0.5 (0.0)	0.5 (0.0)
Median number of ECTs, n (IQR)	8 (4)	8 (4)	8 (4)	8 (4)	8 (4)	8 (4)	8 (4)	8 (4)	8 (4)

n: number of patients, IQR: interquartile range, ECT: electroconvulsive therapy, s: seconds, ms: milliseconds

Table 2
Numbers and proportions of patients with response and subjective memory impairment at assessment after electroconvulsive treatment and odds ratios for the association between the comorbid diagnoses and these outcomes

		No comorbidity	Personality disorder	Anxiety disorder	Alcohol use disorder
Response CGI-I*	**n (%)**	2 452 (84.9)	281 (62.7)	789 (73.5)	243 (77.1)
	OR (95 % CI)	1 (ref.)	0.30 (0.24–0.37)	0.49 (0.42–0.58)	0.60 (0.45–0.80)
	aOR† (95% CI)	1 (ref.)	0.43 (0.34–0.55)	0.61 (0.51–0.73)	0.75 (0.57–1.01)
Subjective memory impairment**	**n (%)**	359 (15.6)	76 (20.7)	171 (20.6)	41 (16.9)
	OR (95 % CI)	1 (ref.)	1.41 (1.07–1.86)	1.40 (1.14–1.71)	1.10 (0.76–1.55)
	aOR‡ (95% CI)	1 (ref.)	1.03 (0.76–1.37)	1.20 (0.97–1.47)	1.03 (0.71–1.47)

n: number of patients, OR: odds ratio, aOR: adjusted odds ratio, CI: Confidence interval

* A rating of 1 or 2 on the Clinical Global Impression - Improvement Scale (CGI-I)

** A change of ≥ 2 points on the memory item from the Comprehensive Psychopathological Rating Scale

† Adjusted for age and depression severity

‡ Adjusted for gender, age, and depression severity

six ECT sessions with those receiving more sessions, there was no significant difference in subjective memory impairment (14.9% vs. 20.7%, χ^2 (1) = 1.6, P = .20).

4. Discussion

4.1. Key results

In this nation-wide study, we found that depression with a comorbid personality disorder or anxiety disorder was associated with lower odds of response to ECT. Age and depressive episode severity had a similar effect on the odds of response as the comorbidities, implying a reduced impact of comorbidity with higher age and increased severity of depression. We found no difference in subjective memory impairment after ECT in patients with or without comorbidity.

4.2. Strength and limitations

There are several limitations to this study. The ECT treatments were carried out in a number of different facilities in Sweden and there are certain differences in treatment routines between clinics, as well as different routines for assessment and reporting to SNQR-ECT. As the diagnoses were retrieved from the National Patient Register, there was no information on how they were established or on their validity. We did assume that there was a cautious selection of patients for ECT and that the diagnostic process reflected that. We did not differentiate between subtypes of personality disorders or different anxiety disorders, and thus were not able to see if they correlated differently with ECT response. Nor did we have information on the severity of the comorbid disorders. There was no assessment of inter-rater reliability of the CGI-I assessments, as these were made by the local psychiatrists responsible for the patients. Response was assessed within the first week after ECT and there was no information on the duration of improvement. CPRS-M is a subjective measure of memory impairment, which does not cover all aspects of memory disturbances. Another important limitation was the lack of data on general baseline cognitive performance, apart from the self-reported CPRS-M before ECT, due to the use of registry data.

The cross-sectional study design included only patients with reported ratings on our outcome measures and who had completed at least six ECT sessions. This may hamper generalisability, as we cannot know why other patients did not have ratings or why they discontinued treatment. As both the occurrence of comorbid conditions and the outcomes of interest were assessed at the time of follow-up, inference about their temporal relationships should be made with caution (Sedgwick, 2014).

The strengths of this study were that the large sample and the community setting promote generalisation of the results to everyday

Table 3
Numbers, proportions, and odds ratios for the variables in the adjusted analyses for response at assessment after electroconvulsive treatment

	No comorbidity			Personality disorder			Anxiety disorder			Alcohol use disorder		
Response CGI-I*	n (%)	aOR (95 % CI)	P†	n (%)	aOR (95 % CI)	P†	n (%)	aOR (95 % CI)	P†	n (%)	aOR (95 % CI)	P†
Age, years			<.001			<.001			<.001			<.001
18–29	265 (72.6)	1 (ref.)		61 (45.9)	1 (ref.)		121 (54.3)	1 (ref.)		24 (55.8)	1 (ref.)	
30–44	423 (80.4)	1.55 (1.13–2.14)		102 (68.0)	1.76 (1.35–2.30)		229 (75.8)	1.99 (1.56–2.53)		65 (80.2)	1.74 (1.29–2.34)	
45–59	606 (84.5)	1.97 (1.45–2.69)		86 (74.1)	2.21 (1.69–2.89)		252 (81.0)	2.44 (1.92–3.11)		100 (82.6)	2.18 (1.63–2.90)	
≥60	1 158 (90.5)	3.07 (2.27–4.15)		32 (65.3)	3.09 (2.37–4.05)		187 (78.6)	3.19 (2.51–4.05)		54 (77.1)	3.08 (2.32–4.08)	
Depression severity			<.001			<.001			<.001			<.001
Moderate	343 (78.7)	1 (ref.)		57 (53.8)	1 (ref.)		129 (64.2)	1 (ref.)		55 (73.3)	1 (ref.)	
Severe without psychosis	1 299 (81.7)	1.24 (0.94–1.61)		178 (63.1)	1.27 (1.01–1.60)		474 (71.4)	1.31 (1.06–1.61)		155 (76.7)	1.22 (0.95–1.55)	
Severe with psychosis	810 (94.0)	3.75 (2.61–5.43)		46 (76.7)	3.51 (2.55–4.88)		186 (89.0)	3.99 (2.96–5.40)		33 (86.8)	3.62 (2.57–5.14)	

n: number of patients, aOR: odds ratio adjusted for age and depression severity, CI: Confidence interval
* A rating of 1 or 2 on the Clinical Global Impression - Improvement Scale (CGI-I)

† P-values from log likelihood-ratio tests, assessing the variables age and depression severity in the adjusted model

Table 4
Numbers, proportions, and odds ratios for the variables in the adjusted analyses for subjective memory impairment at assessment after electroconvulsive treatment

	No comorbidity			Personality disorder			Anxiety disorder			Alcohol use disorder		
Subjective memory impairment*	n (%)	aOR (95 % CI)	P†	n (%)	OR (95 % CI)	P†	n (%)	OR (95 % CI)	P†	n (%)	OR (95 % CI)	P†
Gender			<.001			<.001			<.001			<.001
Female	226 (17.9)	1 (ref.)		290 (19.1)	1 (ref.)		357 (20.1)	1 (ref.)		253 (18.6)	1 (ref.)	
Male	133 (12.8)	0.67 (0.53-0.85)		145 (12.6)	0.63 (0.50-0.78)		173 (12.7)	0.58 (0.48-0.71)		147 (12.4)	0.62 (0.49-0.77)	
Age, years			<.001			<.001			<.001			<.001
18–29	59 (21.0)	1 (ref.)		85 (21.7)	1 (ref.)		96 (21.1)	1 (ref.)		65 (20.6)	1 (ref.)	
30–44	88 (21.3)	0.99 (0.68-1.44)		118 (22.0)	1.04 (0.76-1.44)		150 (23.3)	1.14 (0.85-1.53)		103 (21.7)	1.05 (0.74-1.49)	
45–59	88 (15.0)	0.68 (0.47-0.99)		106 (15.6)	0.74 (0.53-1.02)		130 (15.7)	0.74 (0.55-1.00)		103 (15.1)	0.71 (0.50-1.01)	
≥60	124 (12.1)	0.54 (0.38-0.76)		126 (11.8)	0.54 (0.39-0.74)		154 (12.8)	0.59 (0.44-0.79)		129 (12.0)	0.54 (0.39-0.76)	
Depression severity			.006			.008			.05			.02
Moderate	50 (13.6)	1 (ref.)		72 (15.9)	1 (ref.)		86 (15.9)	1 (ref.)		63 (14.9)	1 (ref.)	
Severe no psychosis	229 (18.1)	1.43 (1.03-2.02)		279 (18.6)	1.25 (0.94-1.67)		332 (18.8)	1.26 (0.97-1.65)		253 (17.8)	1.27 (0.94-1.73)	
Severe with psychosis	80 (11.9)	0.96 (0.66-1.42)		84 (11.7)	0.83 (0.59-1.18)		112 (13.6)	0.98 (0.72-1.35)		84 (12.0)	0.89 (0.62-1.27)	

n: number of patients, aOR: odds ratio adjusted for gender, age, and depression severity, CI: Confidence interval
* A change of ≥ 2 points on the memory item from the Comprehensive Psychopathological Rating Scale

† P-values from log likelihood-ratio tests, assessing the variables gender, age, and depression severity in the adjusted model

clinical work.

4.3. Interpretation and comparison with previous literature

The ECT given to the comorbidity groups was similar as that given to the total sample, regarding median number of sessions and median pulse width. There were no clinical differences in median seizure duration. The overall short-term response rate in the sample was in the same range as in earlier clinical studies of ECT effectiveness (Prudic et al., 2004; van Diermen et al., 2018). A potential problem with interpretation of the outcomes in this study is if multiple comorbidities have an additive negative effect on the probability for response. To control for this, the two other comorbidities were added to the adjusted logistic regression analyses, but this did not affect the result in any case.

There are a few earlier studies examining response to ECT for depression in patients with comorbid personality disorder, where the very first studies included only a handful of patients with personality disorder (Rasmussen, 2015). In studies from the last decades, results indicate lower response rate after ECT for depression in patients with comorbid personality disorder; our results are consistent with that. The majority of these studies were chart reviews, and only a few were clinical studies with structured assessments to establish personality disorder

diagnosis (Rasmussen, 2015). One exception is a recent chart review that could not detect any significant differences in ECT response for patients with high and low scores on a screening instrument for borderline personality disorder, which used change in Patient Health Questionaire-9 as the outcome measure (Lee et al., 2019). In three earlier studies, adjustments were made for age and presence of psychotic features (Brus et al., 2017a; Feske, 2004; Sareen et al., 2000), but – to our knowledge – none have adjusted for depressive episode severity. When controlling for the depressive episode severity and age in our study, those factors had a substantial impact on the probability of a favourable outcome, reflected in similar odds ratios as those for personality disorder diagnosis.

Our result of lower response rate after ECT for patients with comorbid anxiety disorder is consistent with a study based on the same register and using the Montgomery-Åsberg Depression Rating Scale as outcome (Brus et al., 2017a), but dissimilar to an earlier study from SNQR-ECT also using CGI-I as measure for response (Nordenskjöld et al., 2012). The latter study compared depressed patients with anxiety disorder with patients without anxiety disorder, regardless if they had other comorbidity diagnoses. In our study, the comparison was between patients with the comorbidity of interest and patients without any of the investigated comorbidities, which might explain the differing results. Concomitant alcohol use disorder was not associated with a lower response rate in our study. Nor was alcohol use disorder associated with better outcome in our study, as was the case in a recent study (Aksay et al., 2017). This chart review included only 30 patients with alcohol use disorder and had no structured assessment of response, which might contribute to the differences in our findings.

There are factors that complicate evaluation of ECT response in depression with concurrent comorbidities. One such factor is diagnostic validity; as many symptoms overlap, the presence of psychiatric comorbidity could cause overestimation of depressive episode severity or even lead to a misdiagnosis of a major depressive episode (Beatson and Rao, 2013). An incorrect diagnosis and resulting incorrect ECT indication will lower the rates for successful treatment with ECT. Another factor that may explain lower rates of response and remission in psychiatric comorbidity is the manner in which these outcomes are assessed and defined. Most earlier studies of ECT for patients with comorbid psychiatric disorders have used structured depression symptom scales to assess efficacy, predominantly the Hamilton Rating Scale for Depression (HRSD) (Rasmussen, 2015). HRSD may not be adequate for assessing response or remission of depressive episodes in the presence of psychiatric comorbidity; it has been criticised as regards content validity, with suggestions that it captures mainly anxiety symptoms instead of depression (Porter et al., 2017). The reconstructed HRSD from 1987, which has not been used in ECT studies (Rasmussen, 2015), has shown better psychometric properties. However, it is still considerably more difficult to make a distinction between depression and anxiety in comorbid samples (Porter et al., 2017). This implies that the anxiety symptoms captured by the scales could arise from the personality disorders or the anxiety disorders, and not from the depressive episode they are intended to measure. It is likely that the same issue applies to other depression symptom scales, such as Montgomery-Åsberg Depression Rating Scale. Thus, there is a risk that the anti-depressive effect of ECT is underestimated when using such symptom scales in comorbidity groups ().

The CGI-I scale, used in this study, could give a more accurate account of the ECT effect, as it assesses the actual clinical improvement of depression regardless of baseline symptomatology (Guy et al., 1976). On the other hand, the CGI severity scale could be burdened by the same problem as other symptom scales; the physician should rate the patient's severity of illness in relation to that particular patient population, an assessment which may be affected by the patient's comorbidities (Guy et al., 1976). In view of this, it is interesting that the study using the Patient Health Questionaire-9 as outcome, assessing the actual depression criteria, had contradictory result to those of other studies (Lee et al., 2019).

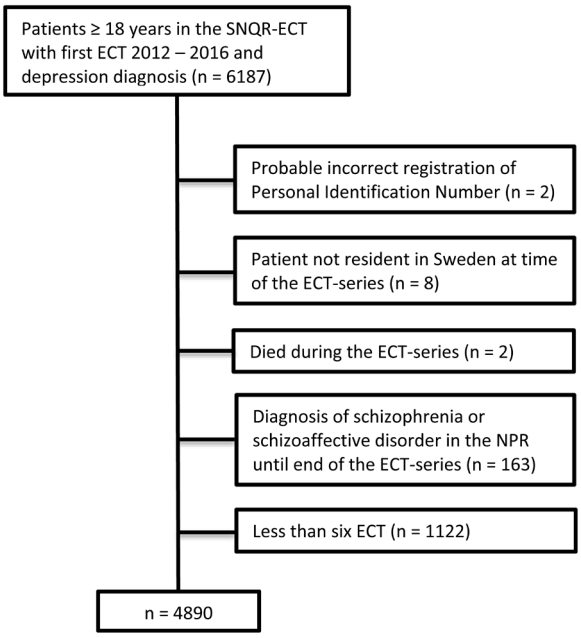

Fig. 1. Study inclusion flow chart.
ECT: electroconvulsive therapy, SNQR-ECT: Swedish National Quality Register for ECT, NPR: National Patient Register, n: number of patients.

The hypothesis of worse subjective memory impairment in presence of psychiatric comorbidity was not confirmed in our study. An important aspect is that major depressive episodes themselves cause cognitive deficits, which are sometimes persistent after remission (Ahern and Semkovska, 2017). This is a confounder in studies of cognitive side effects of ECT, especially since information is rarely available on cognitive functioning before a depressive episode. Alcohol use disorder is also associated with diffuse cognitive deficits, varying with the severity and duration of the disorder and length of abstinence (Crowe et al., 2020; Woods et al., 2016). Further, both personality disorders and anxiety disorders seem to be related to poorer memory functions. (Maurex et al., 2010; Moran, 2016). These aspects were not accounted for in our study; we examined only change in subjective assessment of memory. Subjective memory deficiencies have previously been found to correlate with lower mood rather than objective neuropsychological measurements (Fernie et al., 2014). Therefore, lower response rates after ECT in the personality and anxiety disorder groups might lead to the expectation of worse subjective memory outcome. However, subjective memory was rated within the first week after the ECT course ended, so only immediate impairment was assessed. It is possible that the rating of subjective memory function changes with time.

Patients who received fewer than six ECT sessions had a larger proportion of personality disorder than the included sample overall. The reason for shorter treatment courses in the personality disorder group does not seem to be more subjective impairment in these patients. Although there could be other causes for discontinued ECT, this might suggest that these patients more often receive ECT courses too short to yield a response.

4.4. Clinical implications

Major depressive episodes, regardless of unipolar or bipolar disorders, display high response and remission rates from ECT (Kellner et al., 2020). Though the response rates of ECT in depression in our study are somewhat lower with concurrent personality disorder and anxiety disorder, especially in younger patients and those with less severe depressive episodes, it is still higher than those reported for

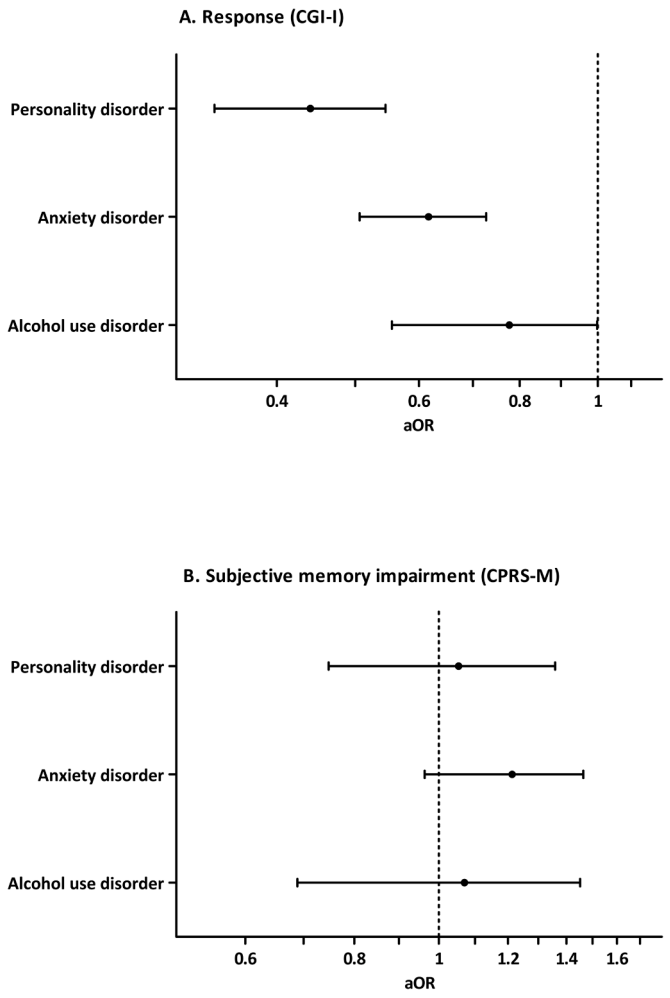

Fig. 2. Adjusted odds ratios (aOR) for the association between the comorbid diagnoses and the outcomes after electroconvulsive treatment (ECT). Panel A displays ORs adjusted for age and depression severity for response defined as a rating of 1 or 2 on the Clinical Global Impression - Improvement Scale (CGI-I). Panel B displays ORs adjusted for gender, age, and depression severity for subjective memory impairment defined as change of ≥ 2 points on the memory item from the Comprehensive Psychopathological Rating Scale (CPRS-M) from baseline to after ECT.

pharmacological treatments and rTMS (Ren et al., 2014; Rush et al., 2006).

In the literature, other factors such as psychotic symptoms, high age, and shorter episode duration consistently support a robust response after ECT, probably alongside melancholic features and psychomotor retardation (Kellner et al., 2020). This implies that the possible negative impact of psychiatric comorbidity on ECT outcome is of less importance and should not exclude patients from treatment with ECT.

Contributors

LS, ET, JP, and RB contributed to the conceptualization of the study. LB undertook registry data management and LS performed the statistical analysis, under supervision from LB. LS and RB drafted the manuscript. All authors provided critical feedback, helped in interpretation of the results and contributed to revising the manuscript. All authors have approved the final manuscript.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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