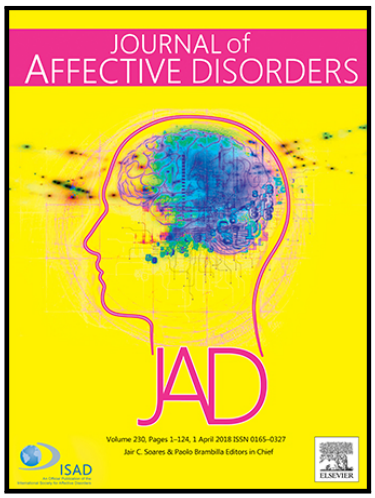

Treatment-resistant depression and suicidality

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HIGHLIGHTS

- Attempted and completed suicide rates are high in treatment-resistant depression.
- No differences in incidences were identified following DBS, VNS or ECT.
- Many clinical trials do not report on suicidal behavior accurately.

Treatment-resistant depression and suicidality

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Abstract

BACKGROUND: Thirty percent of patients with treatment-resistant depression (TRD) attempt suicide at least once during their lifetime. However, it is unclear what the attempted and completed suicide incidences are in TRD patients after initiating a treatment, and whether specific treatments increase or decrease these incidences.

METHODS: We searched PubMed systematically for studies of depressed patients who failed at least two antidepressant therapies and were followed for at least three months after initiating a treatment. We estimated attempted and completed suicide incidences using a Poisson meta-analysis. Given the lack of controlled comparisons, we used a meta-regression to estimate whether these incidences differed between treatments.

RESULTS: We included 30 studies investigating suicidality in 32 TRD samples, undergoing deep brain stimulation (DBS, n=9), vagal nerve stimulation (VNS, n=9), electroconvulsive therapy (ECT, n=5), treatment-as-usual (n=3), capsulotomy (n=2), cognitive behavioral therapy (n=2), ketamine (n=1), and epidural cortical stimulation (n=1). The overall incidence of completed suicides was 0.47 per 100 patient years (95% CI: 0.22 – 1.00), and of attempted suicides 4.66 per 100 patient years (95% CI: 3.53 – 6.23). No differences were found in incidences following DBS, VNS or ECT.

LIMITATIONS: Suicidality is poorly recorded in many studies limiting the number of studies available.

CONCLUSIONS: The attempted and completed suicide incidences are high (0.47 and 4.66 per 100 patient years respectively), but these incidences did not differ between three end of the line treatments (DBS, VNS or ECT). Given the high suicide risk in TRD patients, clinical trials should consider suicidality as an explicit outcome measure.

KEYWORDS: depressive disorder; treatment-resistant; suicide; meta-analysis; systematic review

Introduction

Treatment-resistant depression (TRD) is one of the biggest clinical challenges in psychiatry. Firstly, because of its high prevalence: an estimated 44% of patients do not respond to two consecutive antidepressant therapies, and an estimated 33% do not to four (Rush et al., 2006). Secondly, the remnant symptoms lead to loss of quality of life, decreases in productivity, more hospitalizations and higher health care costs (Gibson et al., 2010; Ivanova et al., 2010; Olchanski et al., 2013). Even more important, TRD is a life-threatening disorder, given the extremely high suicide risk: approximately 30% of the patients attempt suicide at least once in their life time (Dunner et al., 2006; Hantouche et al., 2010; Nelsen and Dunner, 1995). This is at least double the life time rate in non-resistant depression (estimated between 8.4% (Bernal et al., 2007) and 15.9% (Chen and Dilsaver, 1996)) and 15 times higher compared with the 1.8% in the general European population (Bernal et al., 2007; Nock et al., 2008).

Given the high suicide risk of TRD patients, it is of paramount importance to track whether specific treatments might impact suicide risk. A regular treatment for TRD is electroconvulsive therapy (ECT), whereas vagal nerve stimulation (VNS), deep brain stimulation (DBS) and ketamine have emerged as (experimental) alternatives over the last two decades. Of these, ECT and ketamine are assumed to abruptly reduce suicidality (Kellner et al., 2005; Murrough et al., 2015), whereas anecdotal reports associate DBS with suicidal ideation in neurologic patients (Foncke et al., 2006; Mahgoub and Kotbi, 2009).

Unfortunately, the literature does not offer a systematic overview of how many patients with TRD attempt or complete suicide following initiation of a treatment, let alone possible differences between treatments. Therefore, with this review we aim to 1) estimate attempted and completed suicide incidences in TRD patients irrespective of treatment and 2) estimate whether specific treatments might increase or decrease these incidences.

Methods

For this review, we define treatment-resistant depression as patients who failed at least two adequate antidepressant therapies (e.g. psychotherapy, antidepressants). This is based on a recent proposal by Conway et al., who defined two failed therapies as the first stage of TRD given the substantial drop in response rates after two failed treatments (Conway et al., 2017). Besides studies which have failure of at least two treatments as an inclusion criterion, we also include trials on neurosurgical methods (e.g. DBS, VNS), ECT or ketamine. We assume patients in these trials to have failed at least two treatments, unless the study explicitly specified this was not the case. These treatments are considered end of the line treatments and are generally not offered to patients who failed less than two antidepressants. We operationalize suicidality as observable suicidal behaviour, i.e. attempted or completed suicides.

Search strategy and selection criteria

We searched PubMed on May 24, 2017 without date restrictions, with the terms 'depression' AND ('therapy refractory' OR 'treatment resistant' OR 'deep brain stimulation' OR 'electroconvulsive therapy' OR 'nervus vagus stimulation' OR 'ketamine') AND ('suicid*' OR 'clinical trial' OR 'year follow-up'). A language filter was applied, so only studies published in English were retrieved. We included studies when they 1) concerned an original retrospective or prospective study on one or more antidepressant treatments; 2) included adult patients with a primary diagnosis of a major depressive episode; 3) included treatment-resistant patients (see definition above); 4) had a follow up of at least three months; 5) reported attempted or completed suicides, or explicitly stated no serious adverse events were recorded. We additionally included studies in which all participants had a complete follow-up as studies without any completed suicides. Studies were excluded if they 1) included elderly, adolescent or

remitted patients only; 2) included patients with a history of attempted suicide, comorbid substance abuse, or psychotic depression only (since these patients have increased odds of attempting suicide (Beghi et al., 2013; Oquendo et al., 2006; Zalpuri and Rothschild, 2016)); or 3) N≤6 patients. If (sub)samples of patients were discussed in more than one study, we only included the study with the largest sample and/or the longest follow-up.

Analysis

Results are summarized as incidence of completed or attempted suicide per 100 patient years. This reflects the number of recorded cases per 100 years of patients followed. For instance, if 25 patients are followed for one year and 1 suicide attempt is recorded, this sums up to 1 per 25 patient years and consequently, 4 per 100 patient years. This measure allows pooling of studies with different follow-up durations.

Analyses were done separately for attempted and completed suicides, using the 'metafor' package (Viechtbauer, 2010) in R, version 3.3.1 (R Core Team, 2014). Poisson mixed-effects meta-analyses were executed with the natural log incidence as the outcome measure and study as random effect. This model can handle incidence rates of rare events appropriately, given these are positively skewed and have non-normal error rates (Stijnen et al., 2010). In the absence of any randomized or controlled comparisons of treatments, a meta-regression was performed by adding treatment modality as a predictor to investigate the impact of specific treatments on suicidality. To enhance interpretability, the reported incidence rates in the Results section are described as the actual incidence per 100 patient years, i.e. the log incidence rates are transformed with the natural exponential function.

Results

The PubMed search came back with 3046 results, of which we could exclude 2833 on basis of the title and abstract. We inspected the full text of 213 studies, of which we had to exclude 183 for the following reasons: the article did not consider an original study (n=5); the study did not consider TRD patients (n=55); follow-up was less than 3 months (n=27); the study exclusively included adolescents or elderly patients (n=19), patients with previous suicide attempts (n=2) or remitted patients (n=21); N≤6 (n=4); a subsample of an included study was reported (n=12); or the article could not be retrieved (n=7). In addition, we had to exclude 31 studies which followed TRD patients for at least three months, because neither attempted nor completed suicide rates were reported.

We included 30 studies investigating 32 samples (Table 1), exploring DBS (n=9) (Bergfeld et al., 2016; Bewernick et al., 2012; Dougherty et al., 2015; Holtzheimer et al., 2012; Kennedy et al., 2011; Lozano et al., 2012; Malone et al., 2009; Puigdemont et al., 2012; Schlaepfer et al., 2013), VNS (n=9) (Aaronson et al., 2017, 2013; Bajbouj et al., 2010; Christmas et al., 2013; Cristancho et al., 2011; Feldman et al., 2013; Nahas et al., 2005; Rush et al., 2005; Tisi et al., 2014), ECT (n=5) (Ahmadi et al., 2016; Berg, 2010; Gangadhar et al., 1993; Huuhka et al., 2004; Odeberg et al., 2008), treatment-as-usual (n=3) (Aaronson et al., 2017; Feldman et al., 2013; Stewart et al., 2014), capsulotomy (n=2) (Christmas et al., 2011; Lovett et al., 1989), cognitive behavioral therapy (n=2) (Fava et al., 1997; Matsunaga et al., 2010), ketamine (n=1) (Ionescu et al., 2016), and epidural cortical stimulation (n=1) (Kopell et al., 2011). In the meta-regression only three end of the line treatments (DBS, VNS and ECT) were considered, given the scarcity of studies of the other treatments.

Completed suicides

The overall completed suicide incidence is based on 29 samples from 28 studies, consisting of a total of 1720 patients who were followed up for an average of 149.2 weeks. Irrespective of treatment, the overall incidence of completed suicides was 0.47 per 100 patient years (95% CI: 0.22 – 1.00, Figure 1).

Limiting to DBS, VNS and ECT studies only, the overall incidence was 0.72 (0.32-1.61) per 100 patient years. The incidence was 2.01 (0.84-4.85) in DBS studies, 0.33 (0.10-1.13) in VNS studies, and 0.78 (0.13-4.84) in ECT studies. None of the treatments increased or decreased suicide incidences in a statistically significant way (QM(2)=3.1, P=0.22).

Attempted suicides

The overall attempted suicide incidence is based on 19 samples from 18 studies, consisting of a total of 6235 patients who were followed up for an average of 97.5 weeks. Irrespective of treatment, the overall incidence of attempted suicides was 4.66 per 100 patient years (95% CI: 3.53 – 6.23, Figure 2).

Limiting to DBS and VNS studies only the incidence was 5.05 (3.63-7.03) per 100 patient years. No attempted suicide incidences were reported in any of the ECT studies. The incidence was 5.58 (3.19-9.87) in DBS studies, and 4.85 (3.25-7.32) in VNS studies (effect of treatment: QM(1)=0.1, P=0.74).

Discussion

The estimated incidences in TRD patients are 0.47 completed and 4.66 attempted suicides per 100 patient years, irrespective of which treatment is initiated. No evidence was found for systematically increased or decreased incidences in studies following DBS, VNS or ECT.

The incidences are twice and ten times the incidence found in non-resistant patients: 0.22 completed and 0.43 attempted suicides per 100 patient years (Braun et al., 2016). This confirms treatment resistance as a risk factor for (attempted) suicide (Amital et al., 2008; Hantouche et al., 2010; Neuner et al., 2008). It is striking, however, the ratio of completed to attempted suicide is 1:2 in non-resistant and 1:10 in resistant depression. This could be due to the type of treatments in the studies under review, which were mostly last resort treatments such as capsulotomy, DBS, ECT or NVS. These generally include severe patients with an advanced stage of TRD, which might have inflated the estimate of the attempted suicide incidence. Including more common treatment strategies (e.g., tricyclic antidepressants or monoamine oxidase inhibitors) might have given a lower estimate, but we could not identify such trials reporting on suicidal behavior. This problem was characteristic of our search in general: many studies did not report on attempted suicide at all. We had to exclude 31 studies who did follow TRD patients for three months, but did not report suicide incidences. In addition, 12 of the included studies only reported on completed, but not on attempted suicide. Consequently, the attempted suicide incidence is less accurate than it could have been. This stresses the urgent need for accurately recording and reporting of suicidal behavior in clinical trials, especially when TRD patients are concerned.

In addition, the type of suicide attempt is almost never reported, which can be clustered in impulsive, frequent or well-planned (Lopez-Castroman et al., 2016). This prevents specification of underlying moderators of the high suicide risk in TRD. For instance, if a high proportion of suicide attempts were to be classified as impulsive, this could point to decreased impulse control in TRD patients or an increase of impulsiveness dependent on a specific treatment. Alternatively, a subset of TRD patients might attempt suicide frequently, which is associated with comorbid personality disorders (May et al., 2012; Neuner et al., 2008; Oquendo et al., 2006). Patients with TRD often have comorbid

personality disorders (Newton-Howes et al., 2014; Papakostas et al., 2003), which could be the underlying moderator of the high incidences found here. Another possibility is that TRD patients have a realistic perspective on limited therapeutic options for future improvement, which could lead to a higher proportion of well-planned suicide attempts as opposed to non-resistant patients. This is exemplified by two patients in our own study who applied for euthanasia after DBS turned out ineffective, because they did not have other therapeutic options (Bergfeld et al., 2016).

Limitations

The results suggest neither DBS nor VNS nor ECT increases or decreases suicide risk of TRD patients. However, the small number of available studies, most notably of pharmacologic agents, prevents generalization to other treatments. Moreover, the rarity of suicide and the small number of studies limited the power to detect these differences. As mentioned earlier, we had to exclude many studies which did not record or report on attempted and completed suicides. In addition, none of the studies randomized patients to different treatments, excluding a direct comparison between treatments. Two RCTs of DBS in depression did directly compare active and placebo DBS, both of which did not record suicide attempts in the active or placebo phase (Bergfeld et al., 2016; Dougherty et al., 2015). This suggests DBS does not impact suicide risk, although the studies concern a limited number of patients with a maximum follow-up of four months.

Conclusion

The overall suicide risk is high in treatment-resistant depressed patients, but current evidence suggest three end of the line treatments (DBS, NVS or ECT) do not differ considering suicide risk. However, the estimate of suicide risk is hampered by a surprising high number of trials not reporting on suicidality at all. Therefore, we would advise to include suicidal behaviour as an explicit outcome measure in clinical trials of TRD, including the type of (attempted) suicide for identification of possible moderators.

Author contributions

Isidoor Bergfeld, Mariska Mantione and Damiaan Denys were involved in the design of the research question and search strategy, and drafted the manuscript; Isidoor Bergfeld acquired and analysed the data; all authors were responsible for interpretation of the acquired data and analysis, and critically revised the drafted manuscript. All authors have approved the final submitted version of the manuscript.

Declaration of interest

DD is a member of the advisory board of Lundbeck. DD and RS receive occasional fees from Medtronic for educational purposes. All other authors do not declare conflicts of interests.

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Tables and figures

Table 1. Number of suicide attempters and completers reported in included trials

Study	TRD criterion	N	% (bip)	F/M	Age (M)	Age (SD)	Prev AD (M)	Prev AD (SD)	Lft SAT (%)	FU (M weeks)	Att.	Com.	Att (100 patient years)	Com (100 patient years)
Capsulotomy														
Christmas 2011	N/R	20	15.0%	15/5	40.4	N/R	8.1	2.8	0.0%	364.0	N/R	0	N/R	0.00
Lovett 1989	N/R	15	0.0%	N/R	52.2	13	N/R	N/R	N/R	351.0	N/R	0	N/R	0.00
CBT														
Fava 1997	2	19	0.0%	13/6	41.2	10.9	N/R	N/R	N/R	26.8	N/R	0	N/R	0.00
Matsunaga 2010	2	33	0.0%	19/14	41.3	9.2	2.6	N/R	N/R	60.0	N/R	0	N/R	0.00
DBS														
Bergfeld 2016	6	25	0.0%	17/8	53.2	8.4	10.8	3.3	28.0%	51.7	4	0	16.09	0.00
Bewernick 2012	7	11	0.0%	4/7	48.4	11.1	22.2	7.73	27.3%	104.0	1	1	4.55	4.55
Dougherty 2015	5	29	0.0%	12/17	47.7	12	10.8	3.2	N/R	92.3	4	1	7.77	1.94
Holtzheimer 2012	5	10	0.0%	7/3	40	9.3	22	10	50.0%	94.4	1	0	5.51	0.00
Kennedy 2011	4	20	0.0%	11/9	47.4	10.4	N/R	N/R	N/R	182.4	2	2	2.85	2.85
Lozano 2012	4	21	0.0%	13/8	47.3	6.1	N/R	N/R	N/R	52.0	1	1	4.76	4.76
Malone 2009	7	15	6.7%	11/4	46.3	10.8	12.2	N/R	N/R	101.8	0	0	0.00	0.00
Puidgdemont 2012	5	8	0.0%	6/2	47.4	11.3	N/R	N/R	100.0%	52.0	1	0	12.50	0.00
Schlaepfer 2013	6	7	14.3%	3/4	42.6	9.8	21.9	4.7	42.9%	21.6	0	0	0.00	0.00
ECT														
Ahmadi 2016	N/R	92	N/R	78/14	52	12	N/R	N/R	N/R	416.0	N/R	2	N/R	0.27
Berg 2011	N/R	11	0.0%	7/4	41.5	9.8	N/R	N/R	72.7%	81.9	N/R	2	N/R	11.54
Gangadhar 1993	N/R	30	16.7%	20/10	39.6	N/R	N/R	N/R	N/R	79.9	N/R	1	N/R	2.17
Huuhka 2004	2	13	0.0%	9/4	49	7.9	N/R	N/R	N/R	13	N/R	0	N/R	0.00
Odeberg 2008	N/R	41	36.6%	31/10	63	N/R	N/R	N/R	N/R	148.9	N/R	0	N/R	0.00
epCS														
Kopell 2011[a]	4	12	0.0%	6/6	49.2	6	10	1.73	0.0%	95.4	1	0	4.54	0.00
Ketamine														
Ionescu 2016	3	14	0.0%	11/3	50	7.8	8.6	5.3	14.3%	10.6	0	0	0.00	0.00

NVS													
Aaronson 2013	4	310	21.3%	210/100	47.9	10.8	N/R	N/R	45.5%	48.5	12	N/R	4.15	N/R
Aaronson 2017	4	494	27.1%	350/144	48.9	10.12	8.2	3.3	N/R	208.4	N/R	2	N/R	0.10
Bajbouj 2010	2	74	27.0%	50/24	47.4	11.7	3.5	1.3	N/R	78.8	2	2	1.78	1.78
Christmas 2013	4	41	0.0%	27/14	47.7	10.9	8.4	N/R	N/R	52.0	4	1	9.76	2.44
Cristancho 2011	4	15	33.3%	9/6	49	10	N/R	N/R	53.3%	47.1	2	0	14.72	0.00
Feldman 2013[b]	N/R	690	23.9%	504/186	51.9	N/R	N/R	N/R	N/R	104.0	103	N/R	7.46	N/R
Nahas 2005	3	59	27.1%	38/21	46.8	8.7	15.7	7.9	N/R	85.7	3	0	3.09	0.00
Rush 2005[c]	2	235	10.6%	140/95	46.5	9	16	N/R	N/R	45.6	7	1	3.40	0.49
Tisi 2014	4	27	0.0%	9/18	57.4	14	N/R	N/R	N/R	129.0	N/R	0	N/R	0.00
TAU														
Aaronson 2017	4	301	23.6%	211/90	49.9	11.07	7.3	2.9	N/R	157.1	N/R	2	N/R	0.22
Feldman 2013	N/R	4639	30.0%	3155/1484	56.6	N/R	N/R	N/R	N/R	104.0	324	N/R	3.49	N/R
Stewart 2014	2	28	17.9%	15/13	43	11	7	3	0.0%	52.0	N/R	0	N/R	0.00

[a] Gender of 11 patients is reported in the article; [b] Feldman et al reported 15% of 690 patients attempted suicide, equaling to 101-106 patients. In the analysis, we use 103 patients; [c] Gender of 222 patients is reported in the article; TRD criterion refers to number of failed treatments to be eligible for inclusion.

Abbreviations: % (bip)=number of bipolar patients; Att.=Number of suicide attempters; Com.=Number of suicide completers; DBS=Deep Brain Stimulation; ECT=Electroconvulsive Therapy; epCS=epidural Cortical Stimulation; F/M= female/male ratio; FU (M weeks)=mean follow-up in weeks; Lft SAT (%)=percentage of lifetime suicide attempters; N/R=not reported; TAU=treatment-as-usual; VNS=vagal nerve stimulation.

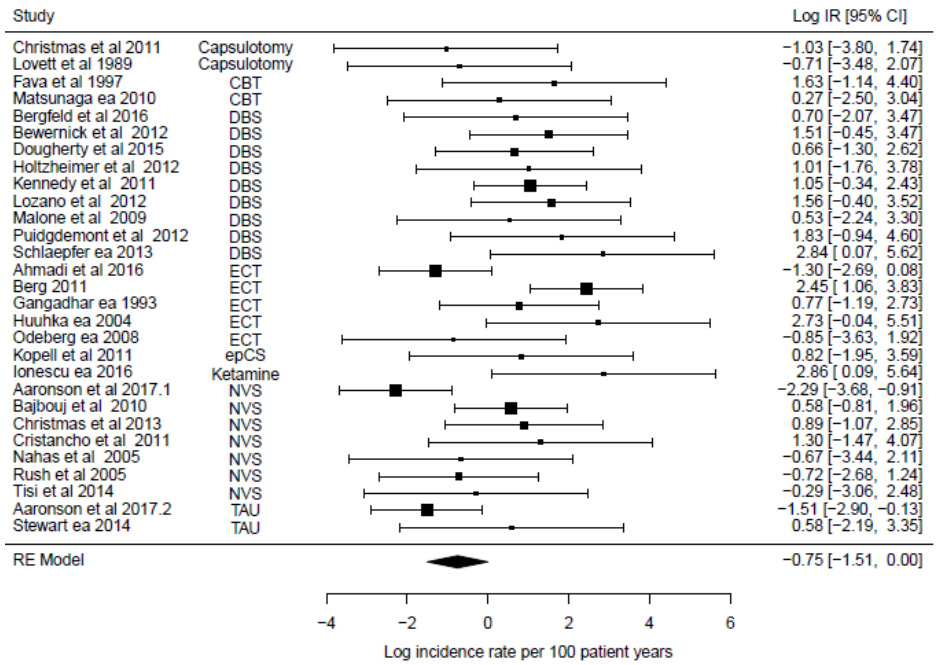

Figure 1. Forest plot of completed suicide incidence

Note the results are presented in natural log incidence rates. The natural exponential (i.e. exp(x)) of the incidence rates results in the actual number of cases per 100 patient years. **Abbreviations:** CBT=cognitive behavioural therapy; CI=confidence interval; DBS=deep brain stimulation; ECT=electroconvulsive therapy; epCS=epidural cortical stimulation; IR=incidence rate; NVS=vagal nerve stimulation; TAU=treatment-as-usual.

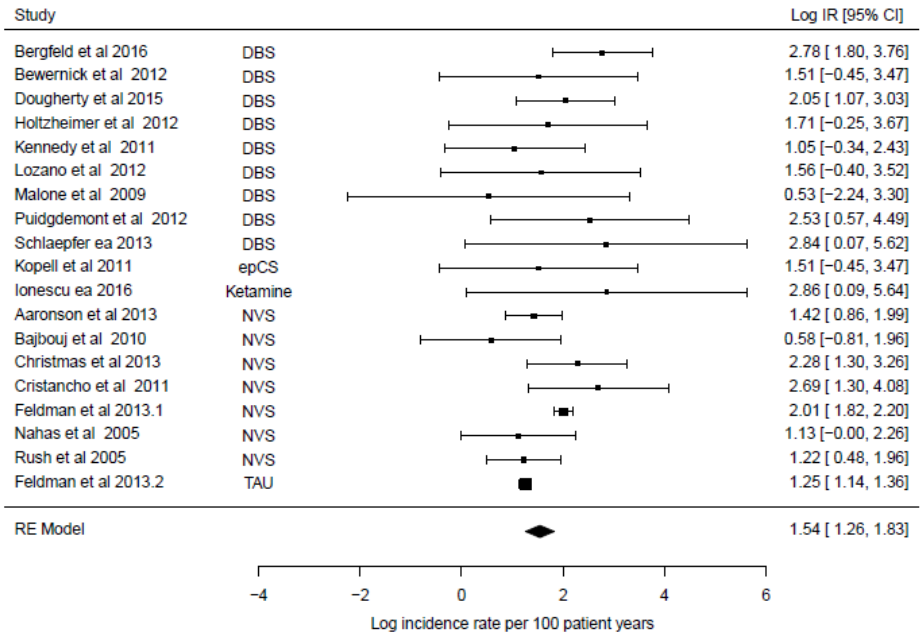

Figure 2. Forest plot of attempted suicide incidence

Note the results are presented in natural log incidence rates. The natural exponential (i.e. exp(x)) of the incidence rates results in the actual number of cases per 100 patient years. **Abbreviations:** CI=confidence interval; DBS=deep brain stimulation; epCS=epidural cortical stimulation; IR=incidence rate; NVS=vagal nerve stimulation; TAU=treatment-as-usual