# Literature Review

## Introduction

There is a need to understand the role of treating depressive disorders on the symptom of suicidality.

There is general consensus that with the start of antidepressant there may be an increase in the risk of suicide within the first two weeks ([Machado-Vieira, Salvadore et al. 2008](#_ENREF_14)). This is sometimes known as the activation syndrome – where the effect of the drugs on certain symptoms such as low energy and agitation precede the effects on hopelessness and mood giving potentially giving rise to increased energy to act on low mood and feelings of hopelessness and potentially increasing the risk of suicidal behaviour ([Rihmer and Akiskal 2006](#_ENREF_19), [Stone, Laughren et al. 2009](#_ENREF_22)). Clinical guidelines stipulate careful monitoring of patients especially the start or change of antidepressant dose if the patient seems susceptible to increased risk of suicide or is under the age of 30 ([Trust 2010](#_ENREF_25)). The longer term effect of treatment – past the activation syndrome phase – is less known ([Fergusson, Doucette et al. 2005](#_ENREF_5), [Hammad, Laughren et al. 2006](#_ENREF_10), [Cuijpers, de Beurs et al. 2013](#_ENREF_4)). The sequence of findings ([Teicher, Glod et al. 1990](#_ENREF_24), [Hammad, Laughren et al. 2006](#_ENREF_10), [Stone, Laughren et al. 2009](#_ENREF_22)) which led to conclusion that one of the potential side-effects of antidepressants may be an increased risk of suicide has meant that more studies are looking to unpick how antidepressants truly effect the symptom of suicidality ([Valuck, Libby et al. 2004](#_ENREF_27), [Witte, Fitzpatrick et al. 2006](#_ENREF_29), [Gibbons, Brown et al. 2012](#_ENREF_6), [Grunebaum, Ellis et al. 2012](#_ENREF_8), [Grunebaum, Keilp et al. 2013](#_ENREF_9), [Coupland, Hill et al. 2015](#_ENREF_2)). Treatment-Emergent Suicide, as these suicide-related drug reactions are known, may occur in a very small percentage of individuals in whom previous suicidality was absent ([Courtet, Jaussent et al. 2014](#_ENREF_3)).

The RCTs which were included the meta-analyses which led to FDA and MHRA warnings on antidepressants (See Appendices for Key Studies) are fraught with limitations. RCTs are not best placed to investigate rare and lethal outcomes such as suicide due to short-term duration and ethical reasons. RCTs have stringent inclusion criteria which excludes severely depressed patients who may be at high risk of suicide. They are designed to cover short periods of time, usually less than a year and it is difficult to assess long term exposure to treatment on suicidality over short periods of time. RCTs are usually limited to a low sample size. With rare outcomes, they may not provide enough power to find an effect. Many of the RCTs and meta-analyses conducted to determine the effectiveness of treatment on suicidality, have included patients with other diagnoses rather than only depression. While this may be more generalizable to the population of interest, this may hinder ascertaining the actual effect of treatment of depression on suicidality. In their systematic review, Fergusson el al found of 702 trials 62.3% had cohorts of less than 100 while 7% went on longer than six months ([Fergusson, Doucette et al. 2005](#_ENREF_5)). In addition, 59% of the trials of SSRIs efficacy were done on diagnoses other than major depression. The inclusion of other diagnoses may render a patient more treatment-resistant or unresponsive to drugs. There are newer views on the underlying bipolar diathesis and that increased suicidality may only be experienced among patients diagnosed with depression but with underlying bipolar diathesis (i.e. they could be future bipolar patients). If examining the role of treatment of depression on suicide, then it patient with any other diagnoses need to be excluded or studied separately. For these reasons, major reviews and meta-analyses can only be tentatively conclusive of the actual effect of antidepressants. Barbui and Gibbons showed that further consideration of realistic factors showed no increased risk of suicide among patients ([Barbui, Esposito et al. 2009](#_ENREF_1), [Gibbons, Brown et al. 2012](#_ENREF_6)).

Relative to studies available on antidepressants and their role in suicide, there are not enough studies examining psychotherapy ([Cuijpers, de Beurs et al. 2013](#_ENREF_4)) and their effects on suicidality. In a systematic review and meta-analyses to investigate the effects of PT on suicidality among adults with depression, Cuijpers et al found 13 studies where the effect of PT was being measured on (3 studies) or hopelessness (11 studies)outcomes. While there is no direct evidence that psychotherapy has an impact on suicidality, the standard guidelines recommend treating milder forms of depression with PT and more severe forms with a combination of psychotherapy and medication ([National Collaborating Centre for Mental Health 2009](#_ENREF_17)).

There are increasing calls for studies to study effects of treatment in the naturalistic clinical environment ([Mann and Kapur 1991](#_ENREF_15), [Rihmer and Akiskal 2006](#_ENREF_19)) and this can be achieved by using clinical research databases. Using clinical registers is now reliable than ever before because there are statistical methods to adjust for the lack of random allocation to a treatment groups by using propensity scores ([Leon, Fiedorowicz et al. 2014](#_ENREF_13)), instrumental variable ([Kim, Eisenberg et al. 2010](#_ENREF_12)) and marginal structural models ([Suominen, Haukka et al. 2009](#_ENREF_23)). In addition, in comparison to trials and other observational studies involving patient recruitment, clinical research databases are larger and offer more power to examine rare conditions/disorders or outcomes. Furthermore, they are longer in duration and their clinical notes provide a rich resource of data. Research using real-life clinical datasets require a fair bit of informatics legwork to acquire a raw dataset.

This review is a presentation of the studies which have examined the role of treatments of depression on suicidality among those with depression using clinical research databases.

## Methods

Inclusion Criteria

The review was conducted separately for adults and young people. Studies were included if the main cohort of study had a diagnosis of depression, exposure was a treatment of depression, at least one of the outcomes (primary or secondary) of interest was the effect of treatment on suicide or suicide related behaviour, the study was conducted in secondary mental health care environment and an anonymised clinical dataset was used. The inclusion criteria were applied for separately for adults and young people. Young people were defined as anyone 25 and below years old to be included in the young people review.

Exclusion Criteria

Studies were excluded if the main study design was an RCT, or an observational study that involved patient recruitment, and pre-determined administered questionnaires, if the study was set in primary care settings or if the main cohort included non-depressive disorders including major depressive disorders.

Data sources and search terms – for adults

Three databases were used to search to look for studies.

*Database 1: OVID SP*

I selected the following databases within OVID SP: MEDLINE(R) 1946 to April Week 2 2015; PsycINFO 1806 to April Week 2 2015; PsycARTICLES Full Text; Embase Classic+Embase 1947 to 2015 April 16; Social Policy and Practice 201503

Final Search Combination

1 and 2 and 9 and 15

1 = "depress\*".ab,hw,id,kf,kw,ot,sh,ti,tx

2 = "suicid\*".ab,hw,id,kf,kw,ot,sh,ti,tx

9 = Longitudinal.ab,hw,id,kf,kw,ot,sh,ti,tx OR observational.ab,hw,id,kf,kw,ot,sh,ti,tx. OR naturalistic.ab,hw,id,kf,kw,ot,sh,ti,tx

15 = "treatment for depression".ab,hw,id,kf,kw,ot,sh,ti,tx OR treatment.ab,hw,id,kf,kw,ot,sh,ti,tx OR therapy.ab,hw,id,kf,kw,ot,sh,ti,tx OR medication.ab,hw,id,kf,kw,ot,sh,ti,tx OR intervention.ab,hw,id,kf,kw,ot,sh,ti,tx

*Database 2: Google Scholar*

Final Search Combination: depression AND suicid\* AND (longitudinal OR naturalistic OR observational) AND (treatment OR therapy)

*Database 3: PubMed*

Final Search Combination:

("Suicide/analysis"[Mesh] OR "Suicide/diagnosis"[Mesh] OR "Suicide/drug effects"[Mesh] OR "Suicide/epidemiology"[Mesh] OR "Suicide/methods"[Mesh] OR "Suicide/mortality"[Mesh] OR "Suicide/pathology"[Mesh] OR "Suicide/prevention and control"[Mesh] OR "Suicide/rehabilitation"[Mesh] OR "Suicide/therapy"[Mesh])

AND "Depressive Disorder"[Mesh]

AND

("Therapeutics/administration and dosage"[Mesh] OR "Therapeutics/adverse effects"[Mesh] OR "Therapeutics/chemically induced"[Mesh] OR "Therapeutics/diagnosis"[Mesh] OR "Therapeutics/diagnostic use"[Mesh] OR "Therapeutics/drug effects"[Mesh] OR "Therapeutics/drug therapy"[Mesh] OR "Therapeutics/epidemiology"[Mesh] OR "Therapeutics/methods"[Mesh] OR "Therapeutics/prevention and control"[Mesh] OR "Therapeutics/psychology"[Mesh] OR "Therapeutics/statistics and numerical data"[Mesh])

Data sources and search terms – for young people

Three databases were used to look for studies.

*Database 1: OVID SP*

I selected the following databases: MEDLINE(R) 1946 to April Week 2 2015, PsycINFO 1806 to April Week 2 2015, PsycARTICLES Full Text, Embase Classic+Embase 1947 to 2015 April 16, Social Policy and Practice 201503

Final Search Combination: 1 and 2 and 9 and 15 and 38

1 = "depress\*".ab,hw,id,kf,kw,ot,sh,ti,tx

2 = "suicid\*".ab,hw,id,kf,kw,ot,sh,ti,tx

9 = Longitudinal.ab,hw,id,kf,kw,ot,sh,ti,tx OR observational.ab,hw,id,kf,kw,ot,sh,ti,tx. OR naturalistic.ab,hw,id,kf,kw,ot,sh,ti,tx

15 = "treatment for depression".ab,hw,id,kf,kw,ot,sh,ti,tx OR treatment.ab,hw,id,kf,kw,ot,sh,ti,tx OR therapy.ab,hw,id,kf,kw,ot,sh,ti,tx OR medication.ab,hw,id,kf,kw,ot,sh,ti,tx OR intervention.ab,hw,id,kf,kw,ot,sh,ti,tx

38 = youth.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, ct, pt, an, tc, id, tm] OR young.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, ct, pt, an, tc, id, tm] OR adolescen\*.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tx, ct, pt, an, tc, id, tm]

*Database 2: Google Scholar*

Final search combination: depression AND suicide\* AND (longitudinal OR naturalistic OR observational) AND (treatment OR therapy) AND (young OR youth OR adolescent\*)

*Database 3: PubMed*

Final search combination

("Suicide/analysis"[Mesh] OR "Suicide/diagnosis"[Mesh] OR "Suicide/drug effects"[Mesh] OR "Suicide/epidemiology"[Mesh] OR "Suicide/methods"[Mesh] OR "Suicide/mortality"[Mesh] OR "Suicide/pathology"[Mesh] OR "Suicide/prevention and control"[Mesh] OR "Suicide/rehabilitation"[Mesh] OR "Suicide/therapy"[Mesh])

AND

"Depressive Disorder"[Mesh]

AND

("Therapeutics/administration and dosage"[Mesh] OR "Therapeutics/adverse effects"[Mesh] OR "Therapeutics/chemically induced"[Mesh] OR "Therapeutics/diagnosis"[Mesh] OR "Therapeutics/diagnostic use"[Mesh] OR "Therapeutics/drug effects"[Mesh] OR "Therapeutics/drug therapy"[Mesh] OR "Therapeutics/epidemiology"[Mesh] OR "Therapeutics/methods"[Mesh] OR "Therapeutics/prevention and control"[Mesh] OR "Therapeutics/psychology"[Mesh] OR "Therapeutics/statistics and numerical data"[Mesh])

AND

("Adolescent"[Mesh] OR “Youth” OR “Young”)

Figure 1: Flow diagram of Screening Papers for Adults

Google Scholar

Pubmed

OVID

Total Included Papers

7

9

20800 (1100 screened)

15

415

17

2856

31 papers Excluded

Review: 1

Ecological: 1

Not using Clinical research dataset: 11

Not exclusively Depression patients: 7

Set in Primary care: 2

Not naturalistic allocation to treatment/RCT: 9

Suicidality is not assessed: 1

Did not specify type of treatment for depression: 2

Figure 2: Flow diagram of Screening Papers for Young People

56 papers Excluded

Review: 14

Not using Clinical research dataset: 3

Not exclusively Depression patients: 1

Set in Primary care: 4

Depression treatment effect not assessed: 18

Suicidality is not assessed: 3

Not naturalistic allocation to treatment/RCT: 7

Not youth: 3

Duplicate: 2

Abstract available only: 1

Total Included Papers

5

OVID

Pubmed

Google Scholar

34

21

1694

6

41

144000 (1100 screened)

## Results

Summary of Included Studies

Based on 2835 and 4371 titles and abstracts for young people and adults respectively we found a total of 9 papers to review – 3 studies included both young and adults ([Olfson, Marcus et al. 2006](#_ENREF_18), [Simon, Savarino et al. 2006](#_ENREF_20), [Miller, Swanson et al. 2014](#_ENREF_16)), 2 dedicated to young people ([Valuck, Libby et al. 2004](#_ENREF_27), [Gibbons, Coca Perraillon et al. 2015](#_ENREF_7)) and 4 for adults ([Sondergard, Lopez et al. 2007](#_ENREF_21), [Suominen, Haukka et al. 2009](#_ENREF_23), [Valuck, Orton et al. 2009](#_ENREF_28), [Valenstein, Kim et al. 2012](#_ENREF_26)). Clinical or psychiatric datasets were used in the form of medical claims databases (6 studies) all based in the US, one US Veterans Affairs database (1 study) and linked national registers (2 studies) based in Finland and Denmark. Table 1 and 2 show the characteristics and results obtained. From youth studies, one study found being on treatment for longer was associated with reduced risk of suicide compared with shorter AD treatment ([Valuck, Libby et al. 2004](#_ENREF_27)). Two studies found no increased risk of suicidal behaviour associated with AD treatment ([Valuck, Libby et al. 2004](#_ENREF_27), [Gibbons, Coca Perraillon et al. 2015](#_ENREF_7)). One study found an increased risk associated with SA and suicide deaths ([Olfson, Marcus et al. 2006](#_ENREF_18)) but this association disappeared among SSRIs. Finally higher initiation doses are associated with higher rates of DSH compared those who start on lower doses ([Miller, Swanson et al. 2014](#_ENREF_16)) but not in adults. Also among adults, one study found AD did not reduce mortality by suicide ([Suominen, Haukka et al. 2009](#_ENREF_23)) and another study found antidepressants had a protective effect for SA ([Sondergard, Lopez et al. 2007](#_ENREF_21), [Valuck, Orton et al. 2009](#_ENREF_28)). Studies combining adults and young people data found either no associated with suicidality ([Olfson, Marcus et al. 2006](#_ENREF_18), [Valenstein, Kim et al. 2012](#_ENREF_26)) or non-specific protective effects of treatment on suicide attempts ([Simon, Savarino et al. 2006](#_ENREF_20)). Apart from one study, no other study examined psychotherapy effects on suicidality.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study Origin: Author, Year** | **N; Age range (Years)** | **Database** | **Diagnosis** | **Suicidality Measure** | **Treatment Exposure** | **Comparisons** | **Description of effect of treatment on suicidality** |
| US: Olfson et al, 2006 | 2915; 19 – 64 | Medical Claims Record | Depressive Disorder | Suicide attempt  Completed suicide | ADs:  Any SSRI  Other AD agents (including TCAs) | Suicide attempts (521) vs Non-suicide attempt controls (2394) | No effect of treatment on suicide attempts. |
| US: Simon and Savarino, 2007 | 109256; <25 | Medical Claims Record | Depression | Suicide attempt | Antidepressants  Psychotherapy | Suicide attempt rate at different phases of treatment in PC and AD treatment | No specific effect of treatment on suicidality. There was a generic lowered risk after start of treatment in all treatment groups. |
| Denmark: Sondergard et al, 2007 | 31422; 18 - 110 | Central Psychiatric Case Register | Depressive Disorder | Completed suicide | Antidepressants | 310 Completed suicides versus 31422 Non-suicides | Multiple prescriptions were associated with reduced suicide risk relative to single prescriptions. |
| US: Valuck et al, 2009 | 52271; - 89 | Medical Claims Record | Depression | Suicide attempt | Antidepressants | 10456 Suicide attempts versus 41815 Non-suicide attempts | Every phase was at higher risk of suicide attempt. Abbreviated (early stop) phase and late maintenance phase were at the lowest risk. |
| Finland: Suominen et al, 2009 | 1820; 41.7 (SD 15.4) | Finnish Clinical registers | Depressed patients | Suicide attempt | Antidepressants | Completed suicide rates among those continuing treatment versus those discontinued | No effect of treatment on completed suicides |
| US: Miller et al, 2014 | 162625; 10 – 64 | Medical Claims Record | Depression | Deliberate self-harm | Antidepressants | Higher does initiation (23668); and modal dose initiation (20065) versus low dose initiation. | No effect of high dose initiation on deliberate self-harm |
| US: Valenstein et al, 2012 | 502179; 40-49 | VA health database | Depression | Completed suicide | Antidepressants | Completed suicide rates during exposure to citalopram versus exposure to other new age ADs | Lower risk of suicide among those on Fluoxetine compared to those on Citalopram |

### Abbreviations: VA = Veterans Affairs; AD = Antidepressants; PC = Psychotherapy; SSRIs = Selective Serotonin Reuptake Inhibitors; TCAs = Tricyclic Agents

Table 1: Included Studies – Characteristics and Summarised Results – Adults

### Table 2: Included Studies – Characteristics and Summarised Results – Young People

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study Origin: Author, Year** | **N; Age range (Years)** | **Database** | **Diagnosis** | **Suicide Outcome** | **Treatment Exposure** | **Comparisons** | **Description of effect of treatment on suicidality** |
| US: Valuck et al, 2004 | 24119; 12 – 18 | Medical Claims Record | MDD | Suicide attempt | ADs:  SSRIs, TCA  Other AD  Multiple AD | Suicide attempts (148) during treatment (SSRIs – 4595; TCA – 45; Other AD – 492;Mulitple AD – 1674) versus Suicide attempts (197) during no treatment (17313) | No effect of treatment on suicidality.  The longer patients were exposed to AD the more protected they were against Suicide attempts. |
| US: Olfson et al, 2006 | 1504; 6 - 18 | Medical Claims Record | Depressive Disorder | Suicide attempt  Completed suicide | ADs:  Any SSRI  Other AD agents (including TCAs) | Suicide attempts (263) vs Non-Suicide attempt controls (1241) | Cases were more likely to be at risk to AD compared to controls. |
| US: Simon and Savarino, 2007 | 23910; <=25 | Medical Claims Record | Depression | Suicide attempt | Antidepressants  Psychotherapy | Suicide attempt rate at different phases of treatment in PC and AD treatment | No specific effect of treatment on suicidality.  There was a generic lowered risk after start of treatment in all treatment groups. |
| US: Gibbons et al, 2015 | Dataset 1: 55284  Dataset 2: 165744; 5 - 17 | Medical Claims records | Depression | Suicide attempt  Self-inflicted injury | Antidepressants | Suicide attempts with AD versus without AD | No effect of treatment on suicidality. |
| US: Miller et al, 2014 | 162625; 10 -24 | Medical Claims Record | Depression | Deliberate self-harm | Antidepressants | Higher than modal 7117; Below modal 14542 versus low dose initiation | High initiating doses were associated with increased risk of subsequent suicide compared to those on low initiating doses. |

Abbreviations: AD = Antidepressants; PC = Psychotherapy; SSRIs = Selective Serotonin Reuptake Inhibitors; TCAs = Tricyclic Agents

Discussion

The studies presented are all methodologically robust and make use of clinical databases well to investigate treatment and suicidality. There were a few recurring results among the studies.

Lack of effect

Compared to young people, more studies showed that was no effect of treatment on suicidality ([Valuck, Libby et al. 2004](#_ENREF_27), [Olfson, Marcus et al. 2006](#_ENREF_18), [Valuck, Orton et al. 2009](#_ENREF_28), [Miller, Swanson et al. 2014](#_ENREF_16)). This is a common conclusion when assessing the association with treatment and outcome of suicidality. The studies concluding this have several limitations such as unable to account for severity of depression, duration, dose or phase of treatment. The finding of a lack of treatment effect is reflected across the literature in the form of contradicting results owing to methodological limitations ([Rihmer and Akiskal 2006](#_ENREF_19), [Jureidini and McHenry 2009](#_ENREF_11), [Valuck, Orton et al. 2009](#_ENREF_28)) or non-specific effects ([Simon, Savarino et al. 2006](#_ENREF_20)). Simon and Savarino showed there was a non-specific protective effect of treatment on suicidality suggesting that any contact with services may reduce suicidal behaviour. This finding has not been replicated. Kyra-Kim ([Kim, Eisenberg et al. 2010](#_ENREF_12)) conducted a study investigating clinical monitoring on risk of suicide and found that with every clinical contact the risk of suicide increased at high risk periods.

Phases of treatment, Duration and Dose of treatment

Studies found that there are phases of treatment or doses of treatment that may be associated with lowered risk of suicidality ([Suominen, Haukka et al. 2009](#_ENREF_23), [Miller, Swanson et al. 2014](#_ENREF_16)) and that the longer the treatment the lower the risk of suicide ([Simon, Savarino et al. 2006](#_ENREF_20), [Valuck, Orton et al. 2009](#_ENREF_28)). This contradicts evidence from RCTs which are limited to shorter observation periods and have shown no effect or increased risk in young people. Coupland and Gibbons have provided support for this in their studies account for time ([Gibbons, Brown et al. 2012](#_ENREF_6), [Coupland, Hill et al. 2015](#_ENREF_2)).

Limitations of using naturalistic datasets and the strength of this project aim

The constant limit in using these datasets is the naturalistic manner in which data is recorded so not all confounding factors are recorded as opposed to a pre-planned questionnaire in studies which require active participant recruitment. The studies included in the review used data variables that were available to them. CRIS, the data source to be used in my PhD, differs from these datasets in that, though it is a naturalistic dataset, most of the information is recorded in free-text clinical notes. What this means is that with the right kind of informatics tools (machine learning or rules based) I can look for all the confounding data I am interested in and can extract all the data variables of interest.

Most of the labour of this PhD will be investing time in extracting data variables. To define them appropriately, to create rules, build a text-mining algorithm and then to implement, test and validate the algorithm. This is a PhD that requires a fair bit of informatics groundwork to extract data to build the dataset.

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