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Non-psychotropic Medication and Risk of Suicide and Attempted Suicide: a Systematic Review

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12th June 2015.

Dear Dr Groves,

We have submitted for your consideration our systematic review entitled 'Non-psychotropic Medication and Risk of Suicide and Attempted Suicide: a Systematic Review'. This review has neither been published nor is under consideration for publication in any other journal but will be disseminated as a poster presentation at the '28th World Congress of the International Association for Suicide Prevention' on 19th June 2015. All authors have contributed to the manuscript and agreed to be cited as co-authors.

This article has previously been reviewed by 'Drug Safety' and the authors revised the manuscript taking into consideration many of the reviewers' comment. The manuscript was also reviewed by 'British Journal of Clinical Pharmacology' and one key suggestion was the need for a quantitative synthesis which we felt was inappropriate given the heterogeneity of included studies; indeed this was a key finding of our systematic review. The journal 'suicide and life threatening behaviour' felt at this time they did not have capacity to accommodate a systematic review.

We are keen to access a varied audience of researchers and clinicians to highlight the need for improved understanding of the risk of suicide associated with medication, independent from the underlying condition. We are therefore extremely grateful for your consideration for publication in BMJ Open.

To our knowledge, no systematic review has been published which presents the groups of medications that have been investigated in observational epidemiological studies in relation to risk of suicide and attempted suicide. We have identified seven groups of non-psychotropic medication which satisfy these criteria. An epidemiological approach is necessary to investigate suicide, which may otherwise be inaccurately estimated from other definitions of suicidality. It is evident that more robust studies are required, which must accurately classify suicide outcomes and control for the effects of psychiatric and physical comorbidities. This will aid understanding of any associations attributed to medication, beyond that of the underlying illness.

Thanks once again for your kind consideration,

Hayley Gorton (on behalf of HC Gorton, RT Webb, N Kapur & DM Ashcroft)

Non-Psychotropic Medication and Risk of Suicide or Attempted Suicide: a Systematic Review

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ABSTRACT

Objectives: To establish which non-psychotropic medications have been assessed in relation to risk of suicide or attempted suicide in observational studies, document reported associations and consider study strengths and limitations.

Design: Systematic Review

Methods: Four databases (Embase, Medline, PsycINFO and International Pharmaceutical Abstracts) were searched from 1990 to June 2014, and reference lists of included articles were hand-searched. Case-control, cohort and case only studies which reported suicide or attempted suicide in association with any non-psychotropic medication were included.

Outcome measures: The outcomes eligible for inclusion were suicide and attempted suicide, as defined by the authors of the included study.

Results: Of 11,792 retrieved articles, 19 were eligible for inclusion. Five studies considered cardiovascular medication and antiepileptics; two considered leukotriene receptor antagonists, isotretinoin and corticosteroids; one assessed antibiotics and another assessed varenicline. An additional study compared multiple medications prescribed to suicide cases versus controls. There was marked heterogeneity in study design, outcome and exposure classification, and control for confounding factors; particularly comorbid mental and physical illness. No increased risk was associated with cardiovascular medications, but associations with other medications remained inconclusive and study heterogeneity precluded quantitative analysis.

Conclusions: Whether non-psychotropic medications are associated with increased risk of suicide or attempted suicide remains largely unknown. Robust identification of suicide outcomes and control of comorbidities could improve quantification of risk associated with non-psychotropic medication, beyond that conferred by underlying physical and mental illnesses.

STRENGTHS AND LIMITATIONS

- This systematic review has identified which non-psychotropic medications have been investigated in observational studies in relation to suicide and attempted suicide.
- Only suicide and attempted suicide outcomes were considered to reduce misclassification, more likely with other definitions of suicidality.
- Study heterogeneity precluded pooling of studies within each group of non-psychotropic medication, or meta-analyses.

INTRODUCTION

Worldwide, approximately 800,000 people die by suicide annually,[1] therefore suicide prevention is an international priority.[2] In addition to being the single strongest predictor of suicide,[1] attempted suicide increases risk of all-cause mortality.[3] A multitude of factors contribute to raised suicide risk,[4, 5] in particular the presence of mental illness.[6, 7] Additionally, the elevated risk of suicide associated with physical illnesses is becoming increasingly recognised, [7-9] albeit to a lesser extent than the risk associated with mental illness.[7]

Although suicide risk differs between physical illnesses,[7] individuals who have been hospitalised for any physical illnesses are at higher risk of suicide than those who have not.[8] A multitude of factors may contribute to increased suicide risk, including disease severity, comorbidities and impact on quality of life. Furthermore, it is largely unknown whether the non-psychotropic medications used to treat physical illnesses influence suicide risk beyond that attributed by the illness itself.

In 2009, 125 medications, some non-psychotropic, had been labelled suicidal ideation or behaviour by the US Food and Drug Administration (FDA).[10] Suicidality outcomes encompass a broad spectrum of suicidal intent, ranging from passive ideation without active planning to harm oneself, to self-harm without intent to die, to unsuccessful attempted suicide, to death by suicide.[11] More commonly occurring suicidality outcomes are used as proxies for suicide and attempted suicide because randomised controlled trials (RCTs) are greatly underpowered to examine these rare outcomes. Therefore, assessment of suicide and attempted suicide in observational studies is essential to examine potential risks posed by non-psychotropic medication independent of the underlying physical illness.

Associations between selected non-psychotropic medications and suicidality have been considered in narrative reviews [12-14] and one systematic review has focused on antiepileptic drugs (AEDs).[15] However, to our knowledge, no systematic review which considers the extent of the associations between all non-psychotropic medications and suicide has been published. We therefore aimed to: (i) identify which non-psychotropic medications have been examined in relation to risk of suicide and attempted suicide in observational studies; (ii) discern what associations have been reported; and (iii) assess the strengths and limitations of these studies.

METHOD

Literature search

Four electronic databases, Embase, Medline, PsycINFO and International Pharmaceutical Abstracts, were independently searched. In all searches, there was a requirement for *suicide* or *suicidal* to be in the title or abstract. Terminology was selected to encompass any non-psychotropic medication; medication not primarily prescribed to treat the mental illnesses described in *Diagnostic and Statistical Manual V*,[16] and operationalised by exclusion of *British National Formulary* categories 4.1-4.4, 4.10.1, 4.10.3 and 4.11.[17] Medication search terms were tailored for each database and required presence in titles or abstracts e.g. Medline: *medicat$, prescriptions, drug prescriptions, pharmaceutical preparations.* Retrieved citations were limited to those published in English between 1990 and June 2014, to encompass any stimulated reporting following a case series of reports regarding suicidality published in 1990.[18] For each medication group identified, additional searches were performed and reference lists of included studies were hand-searched. The full search strategy along with the study protocol is included in *Supplementary Material*.

Study inclusion

One author (HCG) screened studies against inclusion protocol and the other three authors (DMA, RTW, NK) provided advice where a decision to include/exclude was unclear. Observational studies including cohort, case-control, case-crossover and self-controlled case series analyses, which pertained to any non-psychotropic medication and reported suicide or attempted suicide outcomes, separately from other outcomes, were included. Where authors indicated that the outcomes of interest were analysed separately, but only aggregated outcomes were published, personal contact with these authors was made. Case reports, case series, cross-sectional studies, and RCTs were excluded. Any comparison treatment was permitted. Individuals with psychiatric illness were included providing the cohort was not defined by presence of this illness. This is because symptomatic improvement of the mental illness by medication used to treat the illness may preclude detection of any induction of suicidality and prevent equivalent comparison with non-psychotropic use.

Study analysis

Study characteristics, key findings (eg. odds ratios, relative risks) and a critical appraisal, including an assessment of bias, are reported for each study in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-analyses* (PRISMA) statement.[19]

RESULTS

From 11,792 retrieved articles, nineteen empirical studies *(Fig.i)* satisfied our inclusion criteria. A primary focus on psychotropic medication, non-relevant outcomes or alternative study design, accounted for the majority of exclusions. Of the included studies *(Table i)* five studies each explored AEDs [20-24] and cardiovascular medications [25-29] two studies each considered leukotriene receptor antagonists (LTRAs),[30, 31] isotretinoin,[32, 33] and corticosteroids;[34, 35] and one each assessed antibiotics [36] and varenicline.[37] One additional study compared various medications used by individuals who died by suicide, to those used by age and sex-matched controls.[38]

Nine studies reported suicide,[22, 23, 25-30, 38] three reported attempted suicide,[21, 31, 37] two studies presented both outcomes separately [33, 36] and five presented combined outcomes.[20, 24, 32, 34, 35] Some studies linked suicide cases to national [22-25 27-29] or local [38] mortality data, and others relied upon database coding of suicide and attempted suicide.[20, 21, 26, 30-32, 34-37] Studies were conducted in the UK,[20, 26, 30, 34-36] USA,[21, 24, 31, 37] Canada [32, 38] and Scandinavia,[22, 23, 25, 27-29, 33] and therefore were subject to suicide recording conventions adopted by each country. Population sources included healthcare databases which recorded drugs prescribed,[20, 26, 30, 34-36] dispensed,[25, 28, 29] or both;[21, 23, 24, 27, 31, 32, 37, 38] and hospital inpatient [22] or specialist registries.[33]

Thirteen studies accounted for psychiatric comorbidities to various extents.[20, 21, 23-27, 31, 32, 34, 36-38] Statistical adjustment was the most commonly used method. [21, 23-26, 31, 34, 36, 38] Exclusion of patients with history of depression [27] or suicide attempt,[20, 24] stratification by psychiatric history [32] and propensity score matching [24, 37] were also used. In the studies which attempted to mitigate confounding by indication, medication use was restricted to particular conditions,[22, 26, 30-33] stratified by condition [20, 21, 34] or adjustment for physical illness was performed.[20, 23, 24, 38] Some studies quantified suicide risk by comparison of a treated group with an untreated group, [20, 25, 27, 34] the general population [29, 33] or a group using other medications relevant to that condition. [24, 32, 33, 37] Use of an individual as their own control in case-only designs [21, 23, 33, 35] relinquished the need for a separate comparator group.

Study ID & design	Participants	Exposure	Outcome Definition			Adjusted Outcome Measures (95% CI)	Factors Adjusted for in Statistical Analysis	Critique of Study
			Suicide	Attempted Suicide	Combined Suicide & Attempted Suicide			
ANTIEPILEPTIC DRUGS								
Arana et al. 2010; Cohort and case control [20]	THIN, UK, 1/7/1988 - 31/03/2008; Cohort n=5,130,795; first suicide event n=8,212 (completed n=464, attempted n=7,748); Case-control: any suicide event cases n=10,164, controls n=51,005	AED (carbamazepine/ gabapentin/lamotrigine/ levetiracetam/ oxcarbazepine/ pregabalin/tiagabine/ topiramate/valproate/ zonisamide)	-	-	Read codes Suicide: suicidality read code plus code for death in following month and final database activity within 6 months of suicidality code	Cohort study: described incidences Case control study: OR vs. no epilepsy/bipolar/depressive disorder & no AED No epilepsy/bipolar/depressive disorder with AED: 2.57 (1.78-3.71) Epilepsy with AED: 2.31 (1.77-3.02); Epilepsy and no AED: 3.34 (2.34-4.78) OR AED use in epilepsy vs. non-use: 0.59 (0.35-0.98)	Age, disease duration, history: AED/ antidepressant/ lithium/ antipsychotic/ mental illness/ alcohol abuse; chronic disease score Excluded: personal or family history of suicide attempt.	Grouped outcomes: AEDs grouped and proportions of individual AEDs not presented.
Gibbons et al. 2010; Within-subject comparison in a cohort [21]	PharMetrics Patient Centric Database, USA, 2000-2006.Cohort n=131,178; Suicide attempt before initiation n=456, Suicide attempt after initiation n=453	Gabapentin	-	ICD-9 codes E950-959	-	Event Rate Ratio after gabapentin initiation vs. before initiation: Epilepsy: 0.83 (0.34-2.04); Pain disorder: 0.99 (0.78-1.26) Gabapentin monotherapy: 0.53 (0.16-1.73)	Adjustments: age, sex, concomitant diagnosis. Stratified by conditions. Gabapentin monotherapy analysis: excluded individuals with concomitant CNS drugs	Few outcomes in epilepsy and gabapentin monotherapy groups.
Nilsson et al. 2002; Case Control [22]	Stockholm County Council In-Patient Care Register, age>15; epilepsy diagnosis & inpatient 1980-1989. Cases: death before 31/12/1997; age <78; Controls: alive on 31/12/1992 n=171 Suicide & undetermined suicide n=49 (n=24 in analyses)	Controls: phenytoin/ carbamazepine/valproate Cases: any AED	ICD-9 E950-959; ICD-10 X60-X84, Undetermined intent: 980-989; Y10-34	-	-	Relative Risk vs. 1 AED:2 AED: 2.0 (0.8-5.2); 3 AED: 3.1 (0.6-17.5) Relative Risk: Number of dose changes vs 0 dose changes: 1-5 changes: 1.2 (0.4-3.4); Unknown number of dose changes: 13.6 (3.8-49.2)	Age, sex	No adjustment for psychiatric comorbidities. Cases & controls unmatched but similar distributions seen. Controls subject to immortal time bias: AED use required for ≥1 year. Few cases for analyses.
Olesen et al. 2010; Case-crossover analysis and cohort [23]	National Prescription Register, Denmark, 1/1/1997-31/12/2006, age ≥10; covariates identified from Danish National Patient Register. Case-crossover: suicide n= 898; Cohort: newly prescribed AED n=169,725, Suicide n=670 (during treatment n=268)	AED (carbamazepine/ clonazepam/clobazam gabapentin/ lamotrigine/ levetiracetam/ oxcarbazepine/pregabalin /tiagabine/topiramate/ phenobarbitone/ phenytoin/primidone/ valproate/zonisamide)	National Cause of Death Register: ICD-10 X60-X84	-	-	Case-crossover study: OR exposure in case period vs control period: Overall AED: 1.84 (1.36-2.49); carbamazepine: 0.48 (0.21-1.12); gabapentin: 2.20 (0.83-5.83); lamotrigine: 3.15 (1.35-7.34); oxcarbazepine: 0.84 (0.30-2.32); phenobarbital 1.96 (1.02-3.75); valproate: 2.08 (1.04-4.16); topiramate: 2.72 (0.23-32.78) Cohort Study: HR AED initiation vs. carbamazepine: gabapentin:1.27 (0.66-2.44); lamotrigine: 2.09 (1.25-3.50); oxcarbazepine 1.69 (0.81-3.56); valproate: 2.40 (1.42-4.05)	Cohort study: age, sex, socioeconomic status, Charlsons score, civil status, epilepsy / psychiatric disorder, opiate <180 days prior to index date; concomitant antidepressant/ antipsychotic/anxiolytic	Case-crossover design suitability: Exposure may be influenced by indication which may independently increase risk of suicide when exposed to treatment. Exposure: If fewer than seven prescriptions were issued, standard doses were used which may have over- or under-estimated exposure, due to dose variability.
Patorno et al. 2010; Cohort [24]	Healthcore Integrated Research Database, USA; 07/2001-12/2006, age ≥15; new AED Cohort n=297,620 new treatment episodes, Suicide n=26, Suicide Attempt n=801	First exposure to AED (carbamazepine/ ethosuxamide/ felbamate/ gabapentin/lamotrigine/ levetiracetam/ oxcarbazepine/ phenobarbitone/ phenytoin/ pregabalin/ primidone/tiagabine/ topiramate/valproate/ zonisamide)	-	-	Suicide attempt: Emergency department/ hospitalisation ICD-9 E950-E958 Suicide: ICD-10 X60-84	Adjusted HR for suicide and suicide attempt within 180 days of exposure vs. topiramate: carbamazepine: 1.24 (0.77-1.99); gabapentin: 1.42 (1.11-1.80); lamotrigine: 1.84 (1.43-2.37); levetricetam:1.63 (0.84-3.16); oxcarbazepine: 2.07 (1.52-2.80); valproate: 1.65 (1.25-2.19) Propensity score matched HR for suicide and suicide attempt in epilepsy/seizure disorder stratum vs. carbamazepine: gabapentin: 13.92 (1.82-106.38); oxcarbazepine: 0.73 (0.16-3.28); phenytoin: 3.48 (0.97-12.47); topiramate: 0.67 (0.37-1.19); valproate: 0.49 (0.09-2.70)	49 covariates including diagnosis of or medication for: depression, mania, psychosis, anxiety, substance/alcohol abuse, personality disorder, other psychiatric disorders, physical disorders Propensity score matched analysis: in sensitivity analysis	Comparator suitability: Topiramate selected but low frequency of use in epilepsy, although comparison with carbamazepine repeated for this stratum.

CARDIOVASCULAR DRUGS								
Callréus et al. 2007; Nested Case Control [25]	Danish Registry of Cause of Death and The Odense University Pharmacoepidemiological Database, 1991-1998. Suicide Cases n=743, Controls n=14,860	Medications used for lipid lowering, CCB, β-blockers, ACE-I and ARIIB	ICD-8 E950-959, ICD-10 X60-X84, Y87	-	-	OR for current use vs no use: Statin: 1.25 (0.42-3.76); Any lipid lowering drug: 1.21 (0.45-3.28); CCB: 0.96 (0.63-1.48); β-blocker: 0.76 (0.47-1.25); ACE-I: 1.11 (0.68-1.83); ARIIB: 3.52 (1.33-9.30)	Adjustments: ever use of antipsychotics, lithium, antidepressants and drugs for alcohol dependency; use of antidiabetics or AED in past year. Sensitivity analysis: excluded if history of psychotropic drug use	Limited statistical power for some strata.
Gasse et al. 2000; Nested Case Control [26]	GPRD, UK, 01/1991-08/1998, Cases n=38 Controls n=140	Antihypertensive	OXMIS 3009D	-	-	Relative Risk CCB vs other antihypertensive: 0.98 (0.30-3.18)	Body mass index, smoking and history of mental health illness	Potential under ascertainment of suicide outcomes by use of Read codes but this is likely to be non-differential.
Haukka et al. 2012; Cohort [27]	Finish databases: Social Insurance Institution, National Hospital Discharge Register, Causes of Death Register; 01/01/1997-31/12/2005. Exposed n=336,618; Unexposed n=336,618; Suicide n=350	Statin	Cause of Death Register: ICD-10 X60-X84	-	-	Adjusted HR statin exposed vs. unexposed: 0.53 (0.43-0.65) Poisson regression analysis of suicide per years of follow up: 0.5 ≤ 1 year: 0.49 (0.20-1.16);1 ≤ 2 years: 0.59 (0.28-1.25); 2 ≤ 3 years: 0.26 (0.11-0.60); 3 ≤4 years: 0.50 (0.21-1.19)	Adjusted: Sex, age, baseline cardiovascular diseases Additional adjustments in Poisson model: follow-up time, statin group Excluded: history of antidepressant medication	Limited adjustment for confounding factors: particularly psychiatric comorbidity (although individuals with depression excluded). Not generalisable to individuals with depression.
Lindberg et al. 1998; Cohort [28]	Swedish pharmacy data,1988-1989, Cohort n=3,397; CCB n=617, Other cardiovascular medication n=2,780	Cardiovascular medication including CCB (nifedipine/ verapamil/diltiazem/ felodopine)	Swedish Mortality Register: ICD-9 E950-959, E980-989	-	-	7 year suicide risk difference for CCB use vs. non-use: 7.5/1000 person-years (p=0.002) Relative Risk: 5.4 (1.4 – 20.5)	RR adjusted for age and sex.	Limited statistical power: 9 suicides in total. No adjustment for many confounders: including history of mental illness.
Sørensen et al. 2001; Cohort [29]	Pharmacoepidemiological Prescription database of North Jutland County, Denmark, 01/01/1989 -31/12/1995; Cohort n=58,529; Suicide n=104	CCB, β-blocker or ACE inhibitor	National Death Certificate Files: ICD 8/10 codes	-	-	SMR ever-use: β-blocker: 1.6 (1.2-2.1); CCB: 1.2 (0.8-1.7); ACE-I 1.2 (0.7-1.8). SMR use of single study drug: β-blocker: 1.4 (0.9-2.1); CCB: 1.2 (0.7-1.9); 1.2 (0.5-2.4). SMR for β-blocker use only (present and former): low lipid solubility: 0.9 (0.4 -1.9); high lipid solubility: 2.7 (1.7-4.1)	-	Comparison to general population: differences in baseline characteristics and no adjustment for confounders. Potential overestimation of exposure: present use considered for 180 days after prescription received.
LEUKOTRIENE RECEPTOR ANTAGONISTS								
Jick et al. 2009;Cohort [30]	GPRD, UK, 02/1998- 03/2007; Cohort n=23,500	Montelukast	Computer recorded diagnosis	-	-	Suicides in 21,050 person years n=0		No comparison group-would be necessary to compare incidence if cases were identified.
Schumock et al. 2012; Nested Case Control [31]	LifeLink Health Plan Claims Database, USA, 1/1/1997-31/12/2006, asthma & new use of an asthma treatment; age 5-24. Cases n=344 Controls n=3,438	Montelukast, zafrilukast, zileuton	-	ICD-9 code E950-E959	-	Adjusted OR vs never use: Current Use: 0.70 (0.36-1.39), Immediate Past Use: 0.95 (0.36-2.50), Past Use: 0.69 (0.32-1.50). Ever Use: 0.74 (0.46-1.20)	History: bipolar disorder, depression, other mental disorder, substance abuse, suicide attempt; psychological counselling; asthma severity (by proxy).	All cases were exposed to montelukast rather than other drugs in this class (reflects prescribing trends), but results attributed to entire class.
ISOTRETINOIN								
Jick et al. 2000; Cohort [32]	Canadian Saskatchewan Health Database,1983-1997, acne diagnosis and drug exposure; isotretinoin n=7,195, antibiotic n=13,700; suicide or SA n=38 GPRD: data not analysed	Isotretinoin or antibiotic (tetracycline/ erythromycin/ clindamycin/ minocycline/ doxycycline)	-	-	ICD-9 E codes	Relative Risk vs non-exposure: Isotretinoin: current use: 0.9 (0.3-2.4); recent use: 1.1 (0.2-3.7) Antibiotic: current use: 0.8 (0.4-1.7); recent use: 0.5 (0.1-1.4) Relative Risk vs non-exposure in individuals with no psychiatric history: current use: 1.3 (0.3-4.6); recent use: 1.0 (0.1-5.7) Antibiotic: current use: 0.5 (0.1-1.6); recent: 0.7 (0.1-2.7)	Adjusted for & stratified by: Sex, history of psychiatric disorder (depression, psychosis, attempted suicide)	Stratified analysis of individuals with no psychiatric history: small number may limit power. One case omitted and unaccounted for, from analysis of different exposure statuses (n=37).

Sundström et al. 2010; Cohort and crossover analysis [33]	Patient Register (mandatory), Sweden; 1980-1989 (outcomes identified until 2001), aged 15-49, cohort: n=5,756; suicide: n=24; suicide attempt: n=128	Isotretinoin	National cause of death registry (including unclear intent), ICD codes	Suicide attempt hospitalisation ICD-8 & 9 E950-E958, E980-E988: ICD-10 X60-64; Y10-Y34	-	Cohort: Standardised Incidence Ratio for all suicide attempts: isotretinoin users vs general population: 3 years pre-treatment: 0.99 (0.65-1.44); 1 year pre-treatment: 1.57 (0.86-2.63); <6 months post-treatment: 1.78 (1.04-2.85); 3 years post-treatment: 1.04 (0.74-1.43) Case-crossover: Rate difference 1 year pre-treatment vs 6 months post-treatment: 1st attempts: 0.86 (-0.78-2.50) cases/1000 person-years; all attempts: 0.40 (-1.46-2.26) cases/1000 person-years SMR for suicide: incompletely recorded	-	Outcome misclassification possible: Requirement for hospital admission may underestimate suicide attempts. Attribution of suicide attempt to exposure for up to15 years following exposure, may overestimate attempts. Comparison with general population: no control for confounding factors, including confounding by indication.
CORTICOSTEROIDS								
Fardet et al. 2012; Cohort [34]	THIN, UK, 01/01/1990 - 31/12/2008; age ≥18; new glucocorticoid exposure n=372,696; exposed with indication n = 261,272; unexposed n=1,224,984; unexposed matched by indication n=660,776; Exposed groups suicide n=19; suicide attempt n=90	Oral glucocorticoid (prednisolone/prednisone/ hydrocortisone/ dexamethasone/triamcinolone /betamethasone/ methylprednisolone/ deflazacort)	-	-	Read codes and cross-searched death certificates	Adjusted HR: Exposed vs. unexposed: 5.27 (3.82-7.29) Exposed vs unexposed, matched by indication: 6.89 (4.52-10.50)	Adjusted: Age, sex, history neuropsychiatric disorder Separate analysis for cohorts matched by indication.	Handling of repeated courses: random selection of course could alter baseline risk dependent on course selected. If later courses chosen, individual subject to immortal time bias until this time.
Fardet et al. 2013; Cohort & Self-Controlled Case Series [35]	THIN, UK 01/01/1990 - 31/12/2008; age≤18; glucocorticoid use for 1-3 years. Cohort n=991; Suicide or suicide attempt n=6	Oral glucocorticoid (prednisolone/prednisone/ hydrocortisone/ dexamethasone/triamcinolone /betamethasone/ methylprednisolone/ deflazacort)	-	-	Read codes	Incident Rate Ratio in withdrawal period vs. ref. period: 0.62 (0.06-6.92) (ref. period:5-3 months prior to discontinuation)	Within-subject analysis	Inadequate statistical power: only 6 cases of suicide or attempted suicide. Potential immortal time bias: for entry into the cohort, must not have died in first year of glucocorticoid use. To be eligible for both arms of the analysis, any suicides must occur in the withdrawal period.
ANTIBIOTICS (QUINOLONES)								
Jick et al. 1998; Nested Case Control [36]	GPRD, UK, ever exposed to quinolone, 01/01/1991 - 30/4/1995, age 15-84. Cases n=348 (suicide n=13, suicide attempt n= 206) Control n=808	Quinolone or other antibiotic in 1-30 or 31-180 days prior to index date	OXMIS code 3009D	OXMIS code L3009, 9779L, 3009C	-	Relative Risk estimate for suicide attempt vs. non-exposure: quinolone 1-30 days: N/A; quinolone 31-180 days: 0.6 (0.2-1.5); other antibiotic 1-30 days: 1.2 (0.5-2.6); other antibiotic 31-180 days: 0.9 (0.5-1.5) *Non-exposure group: no antibiotic in 180 days prior to index date	Age, sex, history of: depression, suicidal behaviour, insomnia, psychosis, anxiety, alcoholism and epilepsy.	Inadequate statistical power: precluded calculation of risk within first month of quinolone exposure or risk of suicide death. Possible underestimation of suicide & attempted suicide: because 1st recorded event used in multiple outcomes. However, all suicidal ideation comparisons were non-significant.
VARENICLINE								
Gibbons and Mann 2013;Cohort [37]	Military Healthcare System, USA, 01/08/2006-31/08/2007. Cohort treated with varenicline (n=19,933); NRT patches (n=15,867). After matching by propensity score: patients n=26,430; included suicide attempts n=5	Varenicline or NRT patches	-	ICD-9 E950-959	-	OR varenicline vs. NRT in patients for whom propensity score matching was possible: 0.67 (0.11-3.99)	Propensity score matching: age, marital status, race, sex, Charlsons' score, inpatient admissions, psychiatric comorbidity, psychotropic medication,	Limited power: few suicide attempt events (n=5)
OTHER MEDICATION								
Voaklander et al. 2007; Case Control [38]	British Columbia Vital Statistics, Health Insurance Registration File, Pharmacare and Physician Claim File, USA, 01/01/1993-31/12/2002, age ≥ 66, suicide Cases n=602 Controls n=2,999	NSAID, cardiovascular drugs, anticoagulants, ulcer medication, steroids, anti-diabetic agents, narcotic pain killers	ICD-9 E950-E959; ICD-10: X60 – X84	-	-	Unadjusted ORs vs. non-use: Antihypertensive medication: 0.94 (0.67-1.31); Lipid lowering medication: 0.60 (0.28-1.26); Anticoagulants: 1.07 (0.52-2.22); Diuretics: 0.94 (0.66-1.36); Ulcer medication: 1.88 (1.35-2.62); Steroids: 1.33 (0.88-2.00). Fully adjusted OR: Diuretics: 0.49 (0.31-0.76); Narcotic Pain Killers: 2.57 (1.71-3.86).	Fully adjusted analyses: demographics, co-morbidity, medication use	Fully adjusted analysis not done for all medications which suggested significance at the unadjusted level (e.g. ulcer medications).

Table i: Characteristics and critique of included studies Key: ACE-I: Angiotensin Converting Enzyme Inhibitor; ARIIB: Angiotensin Receptor II Blocker; AED: Antiepileptic Drugs; CCB: Calcium Channel Blocker; CNS: Central Nervous System; GPRD: General Practice Research Database; HR: Hazard Ratio; NRT: Nicotine Replacement Therapy; NSAID: Non-steroidal Anti-inflammatory Drug; OR: Odds Ratio; OXMIS: Oxford Medical Information System; SMR: Standardised Mortality Ratio; THIN: The Health Improvement Network

Antiepileptic drugs (AEDs)

Of the five studies which investigated AEDs, two reported suicide,[22, 23] one estimated risk of attempted suicide [21] and two combined both outcomes.[20, 24] Four studies utilised a cohort design, [20, 21, 23, 24] one of which also performed a case-crossover analysis [23] and another a within-subject comparison.[21] Additionally, Arana et al.[20] utilised a case-control study, the only design used by Nilsson et al.[22] Some studies considered individual AEDs,[21, 23, 24] whereas others assessed all AEDs combined.[20, 22] Comparisons were made with non-exposure,[20] particular AEDs [23, 24] or multiple AEDs compared to monotherapy in individuals diagnosed with epilepsy.[22]

The association between AEDs and suicide remains undetermined and varies between individual AEDs. Arana et al. reported an increased risk of suicide and attempted suicide when AEDs were used for conditions other than epilepsy, bipolar disorder or depression; compared to controls who did not receive AEDs nor had these diagnoses (OR: 2.57 [95% CI 1.78-3.71]). Conversely, within the epilepsy strata, a reduced risk was identified in the treated group compared to the untreated group (OR 0.59 [95% CI 0.35-0.98]).[20]

Three studies considered risk attributed to individual AEDs. Patorno et al.[24] suggested an increased risk of suicide and attempted suicide associated with gabapentin compared to topiramate (HR 1.42 [95% CI 1.11-1.80]).[24] Conversely, both Gibbons et al.[21]and Olesen et al.[23] reported no statistically significant difference in suicide attempt rate before or after gabapentin initiation. Patorno et al.[24] reported an increased risk of suicide and attempted suicide with valproate and lamotrigine compared to topiramate. However, when compared to carbamazepine in a cohort of people with epilepsy, no elevation in risk was identified whereas Olesen et al.[23] suggested an increased risk of suicide for the same AEDs, when indication was not restricted.

Cardiovascular medications

Two nested case-control studies [25, 26] and three cohort studies [27-29] assessed risk of suicide associated with various cardiovascular medications. In all but one, there was no evidence of association with increased or decreased suicide risk. An initial suggestion of increased risk of suicide with calcium channel blockers (CCB) was made by Lindberg et al. but the reported association was questioned due to small sample size and lack of control for confounding factors [39, 40]. Subsequent studies dismissed any association with CCB use and suicide.[25, 26, 29] Similarly, there was no difference in risk for angiotensin converting enzyme (ACE) inhibitor or β-blocker use compared to non-use [25] during monotherapy versus the general population.[29] An increased

standardised mortality ratio was, however, suggested for highly lipid soluble β-blockers but attributed in part to use in migraine.[29]

An unexpected increased suicide risk with angiotensin II receptor antagonists was reported by Callréus et al. (OR: 3.52 [95% CI 1.33-9.30]),[25] despite control of multiple potential confounding factors. However, few suicides were reported (current use n=5) and, when controlled for psychiatric history, this association became non-significant. Based on the same number of suicide cases, no association between statins and suicide was made. Corroboratively, Haukka et al.[27] suggested no increase in suicide risk in statin users versus non-users, in any follow-up time investigated. When cardiovascular medication use was compared to non-use by Voaklander et al. only diuretics were suggested to significantly influence risk; a protective effect was suggested in the fully adjusted analysis (OR 0.49 [95% CI 0.31-0.76]).[38]

Leukotriene receptor antagonists (LTRAs)

Two observational studies reported that no increased risk of suicide or attempted suicide was apparent when LTRAs, montelukast, zafrilukast and zileuton, were used for the treatment of asthma.[30, 31] No suicides were reported in Jick et al.'s cohort of individuals exposed to montelukast,[30] although one case was retrospectively disqualified based on time lag between exposure and outcome. Similarly, Schumock et al. did not detect any difference in suicide attempt during use of any LTRA compared to non-use in their nested case-control study of individuals diagnosed with asthma, aged 5-24 years.[31]

Isotretinoin

No difference in the combined risk of attempted and completed suicide was associated with isotretinoin or antibiotics, compared to non-exposure, in Jick et al.'s cohort of individuals with acne, regardless of psychiatric history.[32] Similarly, there was no significant difference in attempted suicide risk before treatment compared to six months after treatment, in Sundström et al.'s crossover analysis.[33] On the other hand, when compared to the general population, the highest elevated risk was observed in the first six months of treatment, but this risk was rising prior to medication initiation.

Corticosteroids

No difference in suicide risk was associated with steroid use versus non-use by Voaklander et al.[38] Conversely, in Fardet et al's (2012) cohort study, a five-fold increased risk of suicide and attempted suicide was

reported following glucocorticoid exposure, compared to non-exposure (HR: 5.27 [95% CI 3.82-7.29]) but incidence was low.[34] In a subsequent self-controlled case series, no difference was detected during withdrawal period compared to treatment periods,[35] although this assertion was based on only six cases.

Antibiotics

In the single nested case-control study which focused on quinolone antibiotics, no difference in risk of attempted suicide was detected following exposure to quinolones or other antibiotics, compared to non-exposure.[36]

Varenicline

One cohort study reported suicide attempt, separately from other outcomes, in relation varenicline use. There was no difference in risk during use of varenicline or nicotine replacement patches, when individuals were matched by propensity score.[37]

DISCUSSION

The primary aims of this systematic review were to establish which groups of non-psychotropic medications have been associated with suicide and attempted suicide in observational epidemiological studies; and to quantify the influence these medications have on this risk, beyond that conferred by underlying illness. Overall, the contribution of corticosteroids,[34, 38] isotretinoin [32, 33] and AEDs [20-24] to risk of suicide and attempted suicide remains unresolved whilst there seems no increased risk associated with cardiovascular medications.[25-27, 29] Neither the single studies which investigated quinolones [36] or varenicline,[37] nor the two which assessed LTRAs,[30, 31] suggested an increased risk of suicidality.

With the exception of the cardiovascular medicines, all groups of medications identified in this review have been the subject of FDA or UK Medicines and Healthcare Products Regulatory Agency (MHRA) warnings. In 2008, the FDA warned of an increased risk of suicidal behaviour and ideation during AED use, following a meta-analysis of 199 placebo-controlled RCTs involving 43,892 patients. An overall odds ratio of 1.80 (95% CI 1.24-2.66) was reported.[41] This mainly reflected an increased risk of suicidal ideation and attempted suicide because only four suicides in total were reported across almost two hundred trials. This emphasises the lack of statistical power of RCTs, and even meta-analysis of numerous trials, for examining an outcome as rare as death by suicide. Concerns were raised from medical and research communities regarding the reliability and impact of this warning. The risk was attributed as a class effect despite variation in risk associated with individual AEDs,

there was potential for heterogeneity in outcome designation and there was an unexplained differential risk dependent upon study location.[42, 43] Our review of the observational work which followed is in corroboration with Ferrer et al.'s review, which considered AEDs for any indication, that the association between dying by suicide and AEDs remains inconclusive.[15]

Varenicline is associated with the highest level of warnings issued by the FDA. It may therefore be surprising that only one study which pertains to varenicline is included in this review. This is because no other observational studies considered only suicide or attempted suicide outcomes. Neither observational studies [44, 45] nor a pooled analysis of RCTs which considered all suicidality outcomes suggested an increased risk associated with varenicline,[37] compared to other smoking cessation treatments or placebo. The FDA black-box warning continues to be challenged by the manufacturers of varenicline, based on a meta-analysis of placebo-controlled RCTs.[46] The FDA also warns of suicidal behaviour during use of isotretinoin and in 2014, an expert review in the UK could neither confirm nor discount an association of suicide with isotretinoin.[47] Isotretinoin is one of three non-psychotropic medications on the list of the top twenty medicines most frequently associated with suicide in UK spontaneous reports.[48] The other two medications, efavirenz and mefloquine,[48] carry warnings for suicidal behaviour in their drug monographs.[17] No observational studies reported suicide or attempted suicide outcomes for these medications. Warnings of psychiatric adverse events, including suicidal behaviour, exist for glucocorticoids in the UK, but this group does not feature in the list of FDA drugs linked with suicidal behaviour.[10]

This systematic review has found considerable heterogeneity amongst studies, which makes comparisons both within and between medication groups difficult and quantitative synthesis impossible. All of the studies that considered cardiovascular medications reported suicide only. Conversely, there was variation in reported outcomes within classes of other medications. Some studies reported attempted suicide or combined suicide and attempted suicide outcomes, sometimes because suicide outcomes were too rare to enable detection of difference between groups. Furthermore, different comparison groups were chosen. Schumock et al. controlled for confounding by indication and disease severity by restricting the comparator cohort to people with asthma who use controller medication.[31] On the other hand, comparator group demographics could not be stipulated when standardised mortality rates were estimated.[29]

It is imperative that the underlying risk posed by physical illness as well as pre-existing mental illness or psychological distress is recognised when interpreting any elevation in risk associated with non-psychotropic

medication. This is of particular importance for AEDs because epilepsy has been associated with a two-fold increased risk of suicide compared to the general population.[49] Furthermore, AEDs can be prescribed for a variety of physical and psychiatric conditions including bipolar disorder, which is associated with over a seventeen-fold increased risk of suicide.[7, 50] Additionally, medications may be used for alternative indications where first line treatment has failed. This could contribute to the increased suicide risk observed by Arana et al. when AEDs were prescribed for conditions other than epilepsy, depression or bipolar disorder, much of which was suspected to be indicated for pain.[20] Similarly, Sørensen et al. attributed the increased risk associated with lipid soluble β-blockers in part to the higher prevalence of migraine in this group.[29] Glucocorticoids are often introduced during disease relapse which could contribute to suicide risk, even when indication is controlled for.[34] Likewise, the increased suicide risk identified prior to initiation of isotretinoin, could be a factor of acne severity.[33]

To our knowledge, this is the first systematic review to consider the impact of non-psychotropic medication use on risk of suicide and attempted suicide. Only suicide and attempted suicide outcomes were considered, to minimise outcome misclassification possible when other suicidality outcomes are used as proxies.[11, 13] Determination of an individuals' intent to die by suicide is challenging [51, 52] therefore other terminologies may incorporate suicide attempt. For example, 'non-fatal self-harm' represents a continuum of suicidal and self-harm behaviours with varying motivations and intentions. To avoid overestimation of outcomes, studies were included only if authors explicitly used the label 'suicide attempt'. This may have precluded inclusion of studies which reported attempted suicide as a composite outcome within another definition, and is therefore a limitation of our review. Inclusion of studies from any country introduced further variation in suicide classification.[53] In the UK, open verdicts are conventionally included in epidemiological suicide definitions, as most are deemed to be probable suicides that were not designated as such due to the high burden of proof required in coroners' courts.[54] In other countries, including the United States, open verdicts are generally not included in suicide case definitions. For example, Patorno et al. separately reported violent deaths in their US population, up to 87% of which may be suicides. The trends identified were however similar to those for suicide and attempted suicide outcomes.[24]

Determining the cause of any observed increased risk, specifically as a result of mental or physical illness, the medication itself, or a combination of factors, represents a major challenge. Overall assessments are difficult to report due to variation between study outcomes, populations and control for psychiatric and physical

comorbidities. Robust identification of suicidality outcomes and control of comorbidities is needed in future observational studies, particularly to investigate suicide risk in association with AEDs, isotretinoin and corticosteroids.

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CONFLICTS OF INTEREST

No conflicts of interest are declared

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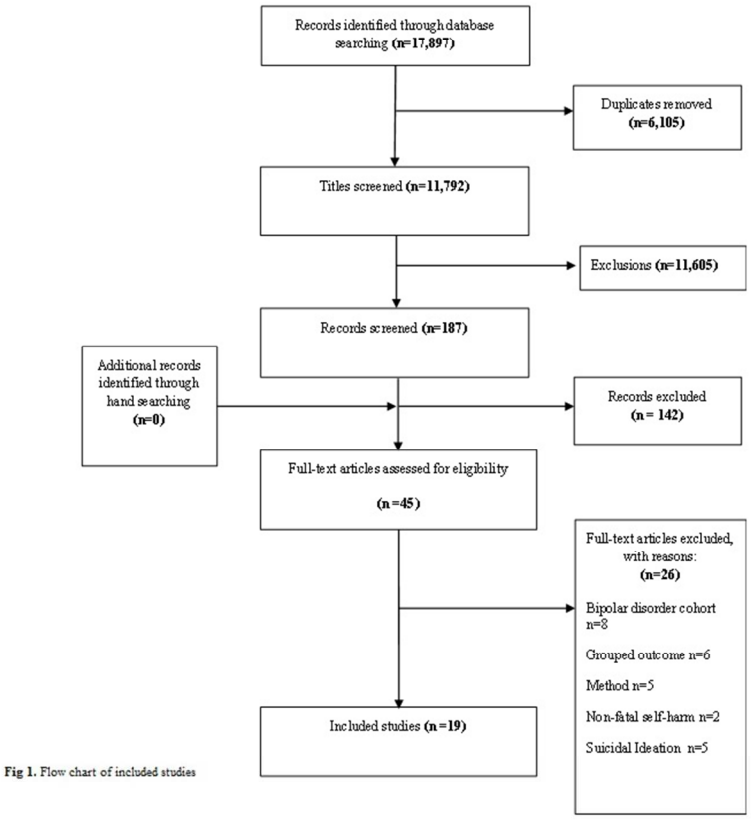

Fig 1. Flow chart of included studies

230x235mm (96 x 96 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	x
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3 and online supplementary material. No interventions specified as RCTs not considered. Open to any comparator in order to address the primary research aims
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Online supplementary material
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3 but nature of research questions warrants relatively unrestrictive criteria
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3. Relevant results which expressed risk of suicide with non-psychotropic medication were accepted, no specific

PRISMA 2009 Checklist

			format was stipulated.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3 and defined in *Table i*
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3. The primary focus was to establish *which* non-psychotropic medications have been associated with suicide. Bias was assessed in the critique *(Table i*) rather than precluding inclusion.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	3 lists examples but is non-exhaustivet. This was to avoid restriction of how risk was presented.
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	n/a, meta-analysis inappropriate for this research question

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	3– selective reporting in studies attempted to be circumvented by personal contact with authors
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	*Fig. 1*
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	*5-7, Table i*
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	*5-7, Table i*

PRISMA 2009 Checklist

Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	*5-7, Table i*
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	*5-7, Table i*
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11-12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10-12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Supplementary Material: Study Protocol

a) Rationale: To assess postulated associations between non-psychotropic medications and suicide risk (increase, decrease or no difference in risk) compared to non-use or use of an alternative medication. Non-psychotropic medication is defined as any medication which does not primarily treat the mental illnesses listed in Diagnostic and Statistics Manual V, and operationally defined by BNF category exclusion of sections 4.1-4.3, [1] 4.4, 4.10.1, 4.10.3 and 4.11.

b) Objectives:

1. Which non-psychotropic medications have been examined, and what associations have been reported, in relation to risk of attempted and completed suicide in observational, epidemiological studies?

2. What are the strengths and limitations of the current studies?

c) Protocol: This protocol was produce in line with PRISMA guidance, but adapted for observational studies.

d) Eligibility Criteria:

i) Population:

- Exposure to any non-psychotropic drug
- Any country: variability in suicide reporting exists between countries and is a limitation when comparing outcomes

Exclusion Criteria:

- Studies entirely in cohorts with mental illness
- Medication as method for overdose
- Illegal or recreational drug use (including alcohol)

ii) Outcome:

- Attempted and completed suicide
- Outcomes of attempted suicide were accepted as this if author used this classification label

Exclusion Criteria:

- Suicidal Ideation
- Aggregated outcomes with no separate analysis of attempted or completed suicide

iii) Study Design:

- Observational design: cohort, case control, nested case control, case-crossover analysis

Exclusion Criteria:

- Randomised Control Trials-unpowered to detect such rare outcomes
- Cross-sectional studies
- Case reports and case series
- Spontaneous reporting systems

v) Year:

- Reports published since 1990- to present. Encompasses inception of large healthcare databased. Provides a reasonable time scale following heightened awareness in 1990, through the infamous case series published by Teicher et al. regarding antidepressants. [2] Study period not stipulated.

vi) Language:

- English

e) Information Sources:

Four databases independently searched with variation in 'medical subject headings' (MESH) and search terms, to account for variation in speciality: *Embase, PsycINFO, Medline and International Pharmaceutical Abstracts.*

Exclusion Criteria:

- Conference abstracts – missing information and lack of peer review
- Grey literature

f) Search Strategy:

In all databases there was a requirement for *suicide* or *suicidal* to be in the title or abstract. The following search terms were used and were required to be included in title or abstract: *medicine* or *medicat$, drug therapy* (exploded) (Embase), *medicat$, prescriptions, drug prescriptions, pharmaceutical preparations* (Medline), *medicat$, medicine, drug$* (PsycINFO*), medicine, medicat$, drug, prescription* (International Pharmaceutical Abstracts).

Citations were collated using *EndnoteX5,* and titles assessed for relevance once duplications removed. Abstracts were then screened and suitable abstracts progressed to full text screening for suitability. Studies which met the inclusion criteria alongside any relevant reviews were hand-searched for relevant citations. For each of the medication groups identified, additional searches were run in the four databases for key words in titles or abstract. In addition to individual drug names for each area, combinations of *calcium channel blockers/blocking agent, beta-blockers, adrenergic beta-antagonists, beta adreno-receptor antagonist, lipid lowering drugs, hydroxymethylglutaryl coenzyme A reductase inhibitor, hypercholesterolemic agent, statin*, *quinolone, fluoroquinolone, 13-cis retinoic acid, glucocorticoid, anticonvulsive, anticonvulsant, antiepileptic* and *varenicline* were searched.

g) Data Extraction: Independently (one investigator, HCG) with advice from DMA, RTW and NK when decision to include or exclude was unclear. Online supplementation referred to, where available.

h) Data Items: List of variables for which data were sought: medication, suicide, suicide attempts, comparator, suicide risk, confounder adjustments

i) Risk of Bias in Individual Studies: Drug exposure classification, outcome definition, population, database suitability, confounding factor adjustment, baseline characteristics

j) Summary measures: Not specified but include odds ratio, hazard ratio, incidence rate ratio, risk ratio, standardised mortality rate, relative risk

k) Risk of bias across studies: Publication bias-negative results or no difference on suicide risk may be less likely to be reported

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Non-psychotropic Medication and Risk of Suicide and Attempted Suicide: a Systematic Review

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Non-Psychotropic Medication and Risk of Suicide or Attempted Suicide: a Systematic Review

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ABSTRACT

Objectives: To establish which non-psychotropic medications have been assessed in relation to risk of suicide or attempted suicide in observational studies, document reported associations and consider study strengths and limitations.

Design: Systematic Review

Methods: Four databases (Embase, Medline, PsycINFO and International Pharmaceutical Abstracts) were searched from 1990 to June 2014, and reference lists of included articles were hand-searched. Case-control, cohort and case only studies which reported suicide or attempted suicide in association with any non-psychotropic medication were included.

Outcome measures: The outcomes eligible for inclusion were suicide and attempted suicide, as defined by the authors of the included study.

Results: Of 11,792 retrieved articles, 19 were eligible for inclusion. Five studies considered cardiovascular medication and antiepileptics; two considered leukotriene receptor antagonists, isotretinoin and corticosteroids; one assessed antibiotics and another assessed varenicline. An additional study compared multiple medications prescribed to suicide cases versus controls. There was marked heterogeneity in study design, outcome and exposure classification, and control for confounding factors; particularly comorbid mental and physical illness. No increased risk was associated with cardiovascular medications, but associations with other medications remained inconclusive and meta-analysis was inappropriate due to study heterogeneity.

Conclusions: Whether non-psychotropic medications are associated with increased risk of suicide or attempted suicide remains largely unknown. Robust identification of suicide outcomes and control of comorbidities could improve quantification of risk associated with non-psychotropic medication, beyond that conferred by underlying physical and mental illnesses.

STRENGTHS AND LIMITATIONS

- To our knowledge, this is the first systematic review to critically evaluate observational studies that have reported suicide and attempted suicide in relation to non-psychotropic medication.
- To reduce misclassification, which is problematic with other broader definitions of suicidality, only suicide and attempted suicide outcomes were considered.
- Study heterogeneity precluded statistical pooling of studies within each group of non-psychotropic medication via meta-analyses.

INTRODUCTION

Worldwide, approximately 800,000 people die by suicide annually,[1] therefore suicide prevention is an international priority.[2] In addition to being the single strongest predictor of suicide,[1] attempted suicide increases risk of all-cause mortality.[3] A multitude of factors contribute to raised suicide risk,[4, 5] in particular the presence of mental illness.[6, 7] Additionally, the elevated risk of suicide associated with physical illnesses is becoming increasingly recognised, [7-9] albeit to a lesser extent than the risk associated with mental illness.[7]

Although suicide risk differs between physical illnesses,[7] individuals who have been hospitalised for any physical illnesses are at higher risk of suicide than those who have not.[8] A multitude of factors may contribute to increased suicide risk, including disease severity, comorbidities and impact on quality of life. Furthermore, it is largely unknown whether the non-psychotropic medications used to treat physical illnesses influence suicide risk beyond that attributed by the illness itself.

In 2009, the US Food and Drug Administration (FDA) required 125 medications, some non-psychotropic, to provide labelled warnings of suicidal ideation or behaviour, or both, in product information.[10] Suicidality outcomes encompass a broad spectrum of suicidal intent, ranging from passive ideation without active planning to harm oneself, to self-harm without intent to die, to attempted suicide, to death by suicide.[11] More commonly occurring suicidality outcomes are used as proxies for suicide and attempted suicide because randomised controlled trials (RCTs) are greatly underpowered to examine these rare outcomes Furthermore, participants of RCTs are closely monitored and study medication will be stopped if serious outcomes are observed. Therefore, assessment of suicide and attempted suicide in observational studies is essential to examine potential risks posed by non-psychotropic medication independent of the underlying physical illness.

Associations between selected non-psychotropic medications and suicidality have been considered in narrative reviews [12-14] and one systematic review has focused on antiepileptic drugs (AEDs).[15] However, to our knowledge, no systematic review which considers the extent of the associations between all non-psychotropic medications and suicide has been published. We therefore aimed to: (i) identify which non-psychotropic medications have been examined in relation to risk of suicide and attempted suicide in observational studies; (ii) discern what associations have been reported; and (iii) critically evaluate the strengths and limitations of these studies.

METHOD

Literature search

Four electronic databases, Embase, Medline, PsycINFO and International Pharmaceutical Abstracts, were independently searched. In all searches, there was a requirement for *suicide* or *suicidal* to be in the title or abstract. Terminology was selected to encompass any non-psychotropic medication. Psychotropic medications exert their main effect on mental symptoms [16] therefore, non-psychotropic medication was accepted as medication not primarily prescribed to treat the mental illnesses described in *Diagnostic and Statistical Manual V*,[17] and operationalised by exclusion of *British National Formulary* categories 4.1-4.4, 4.10.1, 4.10.3 and 4.11.[18] Medication search terms, medical subject headings (MeSH) and explode features were tailored for each database, and required presence in titles or abstracts. The following initial search strategy was used in Embase: suicide or suicidal (ti, ab) AND medicine (ti. ab.) OR medicat* (ti. ab.) OR drug therapy (exp., ti.ab.). Retrieved citations were limited to those published in English between 1990 and June 2014, to encompass any stimulated reporting following a case series of reports regarding suicidality published in 1990.[19] For each medication group identified, additional searches were performed and reference lists of included studies were hand-searched. The full search strategy along with the study protocol is documented in the online Supplementary Material.

Study inclusion

One author (HCG) screened studies against inclusion protocol and the other co-authors (DMA, RTW, NK) provided advice where a decision to include/exclude was unclear. Observational studies including cohort, case-control, case-crossover and self-controlled case series analyses, which pertained to any non-psychotropic medications, were eligible for inclusion. The outcomes of interest were suicide and attempted suicide presented separately or as a combined outcome. Other suicidality outcomes, including suicidal ideation, were excluded. Where authors indicated that the outcomes of interest were analysed separately, but outcomes were published only in combination with other suicidality outcomes, personal contact with these authors was made. Case reports, case series, cross-sectional studies, and RCTs were excluded. Any comparison treatment was permitted. Individuals with psychiatric illness were included providing the cohort was not defined by presence of this illness. This is because symptomatic improvement of the mental illness by medication used to treat the illness may preclude detection of any induction of suicidality and prevent equivalent comparison with non-psychotropic use. It was expected that AEDs would be a group of medicine retrieved by the literature search.

This group does not feature as a class of clinical psychotropic medication per se, but some AEDs would also be classified as mood stabilisers, which are considered psychotropic.[16] To avoid misrepresentation of the scope of non-psychotropic medication investigated in relation to suicide, we included AEDs in this systematic review. However, any study which focussed on the use of AEDs exclusively as mood stabilisers was excluded.

Study analysis

Study characteristics, key findings (eg. odds ratios, relative risks) and a critical appraisal, including an assessment of bias, are reported for each study in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-analyses* (PRISMA) statement.[20] Studies of all quality levels were included in the review and were critiqued by one author (HCG) and discussed at length with co-authors (DMA, RTW). Existing quality assessment tools do not specifically relate to pharmacoepidemiological studies therefore, the criteria outlined in Neyarapally et al.'s quality assessment framework [21] was used to guide the critical evaluation.

RESULTS

From 11,792 retrieved articles, nineteen empirical studies *(Fig.i)* satisfied our inclusion criteria. A primary focus on psychotropic medication, non-relevant outcomes or alternative study design, accounted for the majority of exclusions. Of the included studies *(Table i)* five studies each explored AEDs [22-26] and cardiovascular medications [27-31] two studies each considered leukotriene receptor antagonists (LTRAs),[32, 33] isotretinoin,[34, 35] and corticosteroids;[36, 37] and one each assessed antibiotics [38] and varenicline.[39] One additional study compared various medications used by individuals who died by suicide, to those used by age and sex-matched controls.[40]

Nine studies reported suicide,[24, 25, 27-32, 40] three reported attempted suicide,[23, 33, 39] two studies presented both outcomes separately [35, 38] and five of them combined these outcomes.[22, 26, 34, 36, 37] Some studies linked suicide cases to national [24-27, 29-31] or local [40] mortality data, and others relied upon database coding of suicide and attempted suicide.[22, 23, 28, 32-34, 36-39] Studies were conducted in the UK,[22, 28, 32, 36-38] USA,[23, 26, 33, 39] Canada [34, 40] and Scandinavia,[24, 25, 27, 29-31, 35] and therefore were subject to suicide recording conventions adopted by each country. Population sources included healthcare databases which recorded drugs prescribed,[22, 28, 32, 36-38] dispensed,[27, 30, 31] or both;[23, 25, 26, 29, 33, 34, 39, 40] and hospital inpatient [24] or specialist registries.[35]

Thirteen studies accounted for psychiatric comorbidities to various extents.[22, 23, 25-29, 33, 34, 36, 38-40] Statistical adjustment was the most commonly used method. [23, 25-28, 33, 36, 38, 40] Exclusion of patients with history of depression [29] or suicide attempt,[22, 26] stratification by psychiatric history [34] and propensity score matching [26, 39] were also used. In the studies which attempted to mitigate confounding by indication, medication use was restricted to particular conditions,[24, 28, 32-35] stratified by condition [22, 23, 36] or adjustment for physical illness was performed.[22, 25, 26, 40] Some studies quantified suicide risk by comparison of a treated group with an untreated group, [22, 27, 29, 36] the general population [31, 35] or a group using other medications relevant to that condition. [26, 34, 35, 39] Use of an individual as their own control in case-only designs [23, 25, 35, 37] relinquished the need for a separate comparator group.

Study ID & design	Participants	Exposure	Outcome Definition			Adjusted Outcome Measures (95% CI)	Factors Adjusted for in Statistical Analysis	Critique of Study
			Suicide	Attempted Suicide	Combined Suicide & Attempted Suicide			
ANTIEPILEPTIC DRUGS								
Arana et al. 2010; Cohort and case control [22]	THIN, UK, 1/7/1988 - 31/03/2008; Cohort n=5,130,795; first suicide event n=8,212 (completed n=464, attempted n=7,748); Case- control: any suicide event cases n=10,164, controls n=51,005	AED (carbamazepine/ gabapentin/lamotrigine/ levetiracetam/ oxcarbazepine/ pregabalin/tiagabine/ topiramate/valproate/ zonisamide)	-	-	Read codes Suicide: suicidality read code plus code for death in following month and final database activity within 6 months of suicidality code	Cohort study: described incidences Case control study: OR vs. no epilepsy/bipolar/depressive disorder & no AED No epilepsy/bipolar/depressive disorder with AED: 2.57 (1.78-3.71) Epilepsy with AED: 2.31 (1.77-3.02); Epilepsy and no AED: 3.34 (2.34-4.78) OR AED use in epilepsy vs. non-use: 0.59 (0.35-0.98)	Age, disease duration, history: AED/ antidepressant/ lithium/ antipsychotic/ mental illness/ alcohol abuse; chronic disease score Excluded: personal or family history of suicide attempt.	Grouped outcomes: AEDs grouped and proportions of individual AEDs not presented.
Gibbons et al. 2010; Within-subject comparison in a cohort [23]	PharMetrics Patient Centric Database, USA, 2000-2006.Cohort n=131,178; Suicide attempt before initiation n=456, Suicide attempt after initiation n=453	Gabapentin	-	ICD-9 codes E950-959	-	Event Rate Ratio after gabapentin initiation vs. before initiation: Epilepsy: 0.83 (0.34-2.04); Pain disorder: 0.99 (0.78-1.26) Gabapentin monotherapy: 0.53 (0.16-1.73)	Adjustments: age, sex, concomitant diagnosis. Stratified by conditions. Gabapentin monotherapy analysis: excluded individuals with concomitant CNS drugs	Few outcomes in epilepsy and gabapentin monotherapy groups.
Nilsson et al. 2002; Case Control [24]	Stockholm County Council In-Patient Care Register, age>15; epilepsy diagnosis & inpatient 1980-1989. Cases: death before 31/12/1997; age <78; Controls: alive on 31/12/1992 n=171 Suicide & undetermined suicide n=49 (n=24 in analyses)	Controls: phenytoin/ carbamazepine/valproate Cases: any AED	ICD-9 E950-959; ICD-10 X60-X84, Undetermined intent: 980-989; Y10-34	-	-	Relative Risk vs. 1 AED:2 AED: 2.0 (0.8-5.2); 3 AED: 3.1 (0.6-17.5) Relative Risk: Number of dose changes vs 0 dose changes: 1-5 changes: 1.2 (0.4-3.4); Unknown number of dose changes: 13.6 (3.8-49.2)	Age, sex	No adjustment for psychiatric comorbidities. Cases & controls unmatched but similar distributions seen. Controls subject to immortal time bias [[41]: AED use required for ≥1 year. Few cases- may affect statistical power .
Olesen et al. 2010; Case-crossover analysis and cohort [25]	National Prescription Register, Denmark, 1/1/1997-31/12/2006, age ≥10; covariates identified from Danish National Patient Register; deaths identified from National Cause of Death Registry. Case-crossover: suicide total n=6780, in study period n= 898 Cohort: newly prescribed AED n=169,725, Suicide n=670 during treatment n=268	AED (carbamazepine/ clonazepam/clobazam gabapentin/ lamotrigine/ levetiracetam/ oxcarbazepine/pregabalin /tiagabine/topiramate/ phenobarbitone/ phenytoin/primidone/ valproate/zonisamide)	National Cause of Death Register: ICD-10 X60-X84	-	-	Case-crossover study: OR exposure in case period vs control period: Overall AED: 1.84 (1.36-2.49); carbamazepine: 0.48 (0.21-1.12); gabapentin: 2.20 (0.83-5.83); lamotrigine: 3.15 (1.35-7.34); oxcarbazepine: 0.84 (0.30-2.32); phenobarbital 1.96 (1.02-3.75); valproate: 2.08 (1.04-4.16); topiramate: 2.72 (0.23-32.78) Cohort Study: HR AED initiation vs. carbamazepine: gabapentin:1.27 (0.66-2.44); lamotrigine: 2.09 (1.25-3.50); oxcarbazepine 1.69 (0.81-3.56); valproate: 2.40 (1.42-4.05)	Cohort study: age, sex, socioeconomic status, Charlsons' score, civil status, epilepsy / psychiatric disorder, opiate <180 days prior to index date; concomitant antidepressant/ antipsychotic/anxiolytic	Case-crossover design suitability: Exposure may be influenced by indication which may independently increase risk of suicide when exposed to treatment.
Patorno et al. 2010; Cohort [26]	HealthCore Integrated Research Database, USA; 07/2001-12/2006, age ≥15; new AED Cohort n=297,620 new treatment episodes, Suicide n=26, Suicide Attempt n=801	New exposure to AED (carbamazepine/ ethosuxamide/ felbamate/ gabapentin/lamotrigine/ levetiracetam/ oxcarbazepine/ phenobarbitone/ phenytoin/ pregabalin/ primidone/tiagabine/ topiramate/valproate/ zonisamide)	-	-	Suicide attempt: Emergency department/ hospitalisation ICD-9 E950-E958 Suicide: ICD-10 X60-84	Adjusted HR for suicide and suicide attempt within 180 days of exposure vs. topiramate: carbamazepine: 1.24 (0.77-1.99); gabapentin: 1.42 (1.11-1.80); lamotrigine: 1.84 (1.43-2.37); levetricetam:1.63 (0.84-3.16); oxcarbazepine: 2.07 (1.52-2.80); valproate: 1.65 (1.25-2.19) Propensity score matched HR for suicide and suicide attempt in epilepsy/seizure disorder stratum vs. carbamazepine: gabapentin: 13.92 (1.82-106.38); oxcarbazepine: 0.73 (0.16-3.28); phenytoin: 3.48 (0.97-12.47); topiramate: 0.67 (0.37-1.19); valproate: 0.49 (0.09-2.70)	49 covariates including diagnosis of or medication for: depression, mania, psychosis, anxiety, substance/alcohol abuse, personality disorder, other psychiatric disorders, physical disorders Propensity score matched analysis: in sensitivity analysis	Comparator suitability: Topiramate selected but low frequency of use in epilepsy, although comparison with carbamazepine was repeated for this stratum. Imprecise estimate for gabapentin when restricted to people with epilepsy/seizure disorder: requires cautious interpretation

CARDIOVASCULAR DRUGS								
Callréus et al. 2007; Nested Case Control [27]	Danish Registry of Cause of Death and The Odense University Pharmacoepidemiological Database, 1991-1998. Suicide Cases n=743, Controls n=14,860	Medications used for lipid lowering, CCB, β-blockers, ACE-I and ARIIB	ICD-8 E950-959, ICD-10 X60-X84, Y87	-	-	OR for current use vs no use: Statin: 1.25 (0.42-3.76); Any lipid lowering drug: 1.21 (0.45-3.28); CCB: 0.96 (0.63-1.48); β-blocker: 0.76 (0.47-1.25); ACE-I: 1.11 (0.68-1.83); ARIIB: 3.52 (1.33-9.30)	Adjustments: ever use of antipsychotics, lithium, antidepressants and drugs for alcohol dependency; use of antidiabetics or AED in past year. Sensitivity analysis: excluded if history of psychotropic drug use	Limited statistical power for some strata.
Gasse et al. 2000; Nested Case Control [28]	GPRD, UK, 01/1991-08/1998, Cases n=38 Controls n=140 Nested in cohort of individuals with hypertension diagnosis and prescription for antihypertensive medication	Antihypertensive (including CCB, β-blocker, ACE-I, diuretic)	OXMIS 3009D	-	-	Relative Risk CCB vs other antihypertensive: 0.98 (0.30-3.18)	Body mass index, smoking and history of mental health illness	Potential under ascertainment of suicide outcomes by use of OXMIS codes but this is likely to be non-differential (N.B. at time of publication outcome definition suitable).
Haukka et al. 2012; Cohort [29]	Finish databases: Social Insurance Institution, National Hospital Discharge Register, Causes of Death Register; 01/01/1997-31/12/2005. Exposed n=336,618; Unexposed n=336,618; Suicide n=350	Statin	Cause of Death Register: ICD-10 X60-X84	-	-	Adjusted HR statin exposed vs. unexposed: 0.53 (0.43-0.65) Poisson regression analysis of suicide per years of follow up: 0.5 ≤ 1 year: 0.49 (0.20-1.16);1 ≤ 2 years: 0.59 (0.28-1.25); 2 ≤ 3 years: 0.26 (0.11-0.60); 3 ≤4 years: 0.50 (0.21-1.19)	Adjusted: Sex, age, baseline cardiovascular diseases Additional adjustments in Poisson model: follow-up time, statin group Excluded: history of antidepressant medication	Limited adjustment for confounding factors: particularly psychiatric comorbidity (although individuals with depression excluded). Not generalisable to individuals with depression.
Lindberg et al. 1998; Cohort [30]	Swedish pharmacy data,1988-1989, Cohort n=3,397; CCB n=617, Other cardiovascular medication n=2,780	Cardiovascular medication including CCB , β-blocker, ACE I, diuretic	Swedish Mortality Register: ICD-9 E950-959, E980-989	-	-	7 year suicide risk difference for CCB use vs. non-use: 7.5/1000 person-years (p=0.002) Relative Risk: 5.4 (1.4 – 20.5)	RR adjusted for age and sex.	Limited statistical power: 9 suicides in total. No adjustment for many confounders: including history of mental illness. Indication unknown.
Sørensen et al. 2001; Cohort [31]	Pharmacoepidemiological Prescription database of North Jutland County, Denmark, 01/01/1989 -31/12/1995; Cohort n=58,529; Suicide n=104	CCB, β-blocker or ACE inhibitor	National Death Certificate Files: ICD 8/10 codes	-	-	SMR ever-use: β-blocker: 1.6 (1.2-2.1); CCB: 1.2 (0.8-1.7); ACE-I 1.2 (0.7-1.8). SMR use of single study drug: β-blocker: 1.4 (0.9-2.1); CCB: 1.2 (0.7-1.9); 1.2 (0.5-2.4). SMR for β-blocker use only (present and former): low lipid solubility: 0.9 (0.4 -1.9); high lipid solubility: 2.7 (1.7-4.1)	-	Comparison to general population: differences in baseline characteristics and adjustment for confounders not possible (although some potential confounding factors compared between treatment groups). Potential overestimation of exposure: present use considered for 180 days after prescription received.
LEUKOTRIENE RECEPTOR ANTAGONISTS								
Jick et al. 2009;Cohort [32]	GPRD, UK, 02/1998- 03/2007; Cohort n=23,500	Montelukast	Computer recorded diagnosis	-	-	Suicides in 21,050 person years n=0		No comparison group-would be necessary to compare incidence if cases were identified.
Schumock et al. 2012; Nested Case Control [33]	LifeLink Health Plan Claims Database, USA, 1/1/1997-31/12/2006, asthma & new use of an asthma treatment; age 5-24. Cases n=344 Controls n=3,438	Montelukast, zafrilukast, zileuton	-	ICD-9 code E950-E959	-	Adjusted OR vs never use: Current Use: 0.70 (0.36-1.39), Immediate Past Use: 0.95 (0.36-2.50), Past Use: 0.69 (0.32-1.50). Ever Use: 0.74 (0.46-1.20)	History: bipolar disorder, depression, other mental disorder, substance abuse, suicide attempt; psychological counselling; asthma severity (by proxy).	All cases were exposed to montelukast rather than other drugs in this class (reflects prescribing trends), but results attributed to entire class.
ISOTRETINOIN								
Jick et al. 2000; Cohort [34]	Canadian Saskatchewan Health Database,1983-1997, acne diagnosis and drug exposure; isotretinoin n=7,195, antibiotic n=13,700; suicide or SA n=38 GPRD: data not analysed	Isotretinoin or antibiotic (tetracycline/ erythromycin/ clindamycin/ minocycline/ doxycycline)	-	-	ICD-9 E codes	Relative Risk vs non-exposure: Isotretinoin: current use: 0.9 (0.3-2.4); recent use: 1.1 (0.2-3.7) Antibiotic: current use: 0.8 (0.4-1.7); recent use: 0.5 (0.1-1.4) Relative Risk vs non-exposure in individuals with no psychiatric history: current use: 1.3 (0.3-4.6); recent use: 1.0 (0.1-5.7) Antibiotic: current use: 0.5 (0.1-1.6); recent: 0.7 (0.1-2.7)	Adjusted for & stratified by: Sex, history of psychiatric disorder (depression, psychosis, attempted suicide)	Stratified analysis of individuals with no psychiatric history: small number may limit power. One case omitted and unaccounted for, from analysis of different exposure statuses (n=37).

Sundström et al. 2010; Cohort and crossover analysis [35]	Patient Register (mandatory), Sweden; 1980-1989 (outcomes identified until 2001), aged 15-49, cohort: n=5,756; suicide: n=24; suicide attempt: n=128	Isotretinoin	National cause of death registry (including unclear intent), ICD codes	Suicide attempt hospitalisation ICD-8 & 9 E950-E958, E980-E988: ICD-10 X60-64; Y10-Y34	-	Cohort: Standardised Incidence Ratio for all suicide attempts: isotretinoin users vs general population: 3 years pre-treatment: 0.99 (0.65-1.44); 1 year pre-treatment: 1.57 (0.86-2.63); <6 months post-treatment: 1.78 (1.04-2.85); 3 years post-treatment: 1.04 (0.74-1.43) Case-crossover: Rate difference 1 year pre-treatment vs 6 months post-treatment: 1st attempts: 0.86 (-0.78-2.50) cases/1000 person-years; all attempts: 0.40 (-1.46-2.26) cases/1000 person-years SMR for suicide: incompletely recorded	-	Outcome misclassification possible: Attribution of suicide attempt to exposure for up to15 years following exposure, may overestimate attempts. Comparison with general population: no control for confounding factors, including confounding by indication. This was explored in the case-crossover design.
CORTICOSTEROIDS								
Fardet et al. 2012; Cohort [36]	THIN, UK, 01/01/1990 - 31/12/2008; age ≥18; new glucocorticoid exposure n=372,696; exposed with indication n = 261,272; unexposed n=1,224,984; unexposed matched by indication n=660,776; Exposed groups suicide n=19; suicide attempt n=90	Oral glucocorticoid (prednisolone/prednisone/ hydrocortisone/ dexamethasone/triamcinolone /betamethasone/ methylprednisolone/ deflazacort)	-	-	Read codes and cross-searched death certificates	Adjusted HR: Exposed vs. unexposed: 5.27 (3.82-7.29) Exposed vs unexposed, matched by indication: 6.89 (4.52-10.50)	Adjusted: Age, sex, history neuropsychiatric disorder Separate analysis for cohorts matched by indication.	Handling of repeated courses: random selection of course could alter baseline risk dependent on course selected. If later courses chosen, individual subject to immortal time [41] bias until this time.
Fardet et al. 2013; Cohort & Self-Controlled Case Series [37]	THIN, UK 01/01/1990 - 31/12/2008; age≤18; glucocorticoid use for 1-3 years. Cohort: n=21,995. Eligible for self-controlled case series analysis: n=991; Suicide or suicide attempt n=6	Oral glucocorticoid (prednisolone/prednisone/ hydrocortisone/ dexamethasone/triamcinolone /betamethasone/ methylprednisolone/ deflazacort)	-	-	Read codes	Cohort: incidence rate for suicide or attempted suicide during withdrawal period: 0.03 (0.01-0.2) Self-controlled case series: Incident Rate Ratio in withdrawal period vs. ref. period: 0.62 (0.06-6.92) (ref. period:5-3 months prior to discontinuation)	Within-subject analysis	Inadequate statistical power: only 6 cases of suicide or attempted suicide. Potential immortal time bias [41]: for entry into the cohort, must not have died in first year of glucocorticoid use. To be eligible for the self-controlled case series analysis, any suicides must occur in the withdrawal period.
ANTIBIOTICS (QUINOLONES)								
Jick et al. 1998; Nested Case Control [38]	GPRD, UK, ever exposed to quinolone, 01/01/1991 - 30/4/1995, age 15-84. Cases n=348 (suicide n=13, suicide attempt n= 206 suicidal ideation n=129) Control n=808 (NB. Outcomes analysed separately)	Quinolone or other antibiotic in 1-30 or 31-180 days prior to index date	OXMIS code 3009D	OXMIS code L3009, 9779L, 3009C	-	Relative Risk estimate for suicide attempt vs. non-exposure: quinolone 1-30 days: N/A; quinolone 31-180 days: 0.6 (0.2-1.5); other antibiotic 1-30 days: 1.2 (0.5-2.6); other antibiotic 31-180 days: 0.9 (0.5-1.5) *Non-exposure group: no antibiotic in 180 days prior to index date	Age, sex, history of: depression, suicidal behaviour, insomnia, psychosis, anxiety, alcoholism and epilepsy.	Inadequate statistical power: precluded calculation of risk within first month of quinolone exposure or risk of suicide death. Possible underestimation of suicide & attempted suicide: because 1st recorded event used in multiple outcomes. However, all suicidal ideation comparisons were non-significant.
VARENICLINE								
Gibbons and Mann 2013;Cohort [39]	Military Healthcare System, USA, 01/08/2006-31/08/2007. Cohort treated with varenicline (n=19,933); NRT patches (n=15,867). After matching by propensity score: patients n=26,430; included suicide attempts n=5	Varenicline or NRT patches	-	ICD-9 E950-959	-	OR varenicline vs. NRT in patients for whom propensity score matching was possible: 0.67 (0.11-3.99)	Propensity score matching: age, marital status, race, sex, Charlsons' score, inpatient admissions, psychiatric comorbidity, psychotropic medication,	Limited power: few suicide attempt events (n=5).
OTHER MEDICATION								
Voaklander et al. 2007; Case Control [40]	British Columbia Vital Statistics, Health Insurance Registration File, Pharmacare and Physician Claim File, USA, 01/01/1993-31/12/2002, age ≥ 66, suicide Cases n=602 Controls n=2,999	NSAID, cardiovascular drugs, anticoagulants, ulcer medication, steroids, anti-diabetic agents, narcotic pain killers	ICD-9 E950-E959; ICD-10: X60 – X84	-	-	Unadjusted ORs vs. non-use: Antihypertensive medication: 0.94 (0.67-1.31); Lipid lowering medication: 0.60 (0.28-1.26); Anticoagulants: 1.07 (0.52-2.22); Diuretics: 0.94 (0.66-1.36); Ulcer medication: 1.88 (1.35-2.62); Steroids: 1.33 (0.88-2.00). Fully adjusted OR: Diuretics: 0.49 (0.31-0.76);	Fully adjusted analyses: demographics, co-morbidity, medication use	Fully adjusted analysis not done for all medications which suggested significance at the unadjusted level (e.g. ulcer medications).

Table i: Characteristics and critique of included studies Key: ACE-I: Angiotensin Converting Enzyme Inhibitor; ARIIB: Angiotensin Receptor II Blocker; AED: Antiepileptic Drugs; CCB: Calcium Channel Blocker; CNS: Central Nervous System; GPRD: General Practice Research Database; HR: Hazard Ratio; NRT: Nicotine Replacement Therapy; NSAID: Non-steroidal Anti-inflammatory Drug; OR: Odds Ratio; OXMIS: Oxford Medical Information System; SMR: Standardised Mortality Ratio; THIN: The Health Improvement Network

Antiepileptic drugs (AEDs)

Of the five studies which investigated AEDs, two reported suicide,[24, 25] one estimated risk of attempted suicide [23] and two combined both outcomes.[22, 26] Four studies utilised a cohort design,[22, 23, 25, 26] one of which also performed a case-crossover analysis [25] and another a within-subject comparison.[23] Additionally, Arana et al.[22] utilised a case-control study, the only design used by Nilsson et al.[24] Some studies considered individual AEDs,[23, 25, 26] whereas others assessed all AEDs combined.[22, 24] Comparisons were made with non-exposure,[22] particular AEDs [25, 26] or multiple AEDs compared to monotherapy in individuals diagnosed with epilepsy.[24]

The association between AEDs and suicide remains undetermined and varies between individual AEDs. Arana et al. reported an increased risk of suicide and attempted suicide when AEDs were used for conditions other than epilepsy, bipolar disorder or depression; compared to controls who did not receive AEDs nor had these diagnoses (OR: 2.57 [95% CI 1.78-3.71]). Conversely, within the epilepsy strata, a reduced risk was identified in the treated group compared to the untreated group (OR 0.59 [95% CI 0.35-0.98]).[22]

Three studies considered risk attributed to individual AEDs. Patorno et al.[26] suggested an increased risk of suicide and attempted suicide associated with gabapentin compared to topiramate (HR 1.42 [95% CI 1.11-1.80]).[26] Conversely, both Gibbons et al.[23]and Olesen et al.[25] reported no statistically significant difference in suicide attempt rate before or after gabapentin initiation. Patorno et al.[26] reported an increased risk of suicide and attempted suicide with valproate and lamotrigine compared to topiramate. However, when compared to carbamazepine in a cohort of people with epilepsy, no elevation in risk was identified whereas Olesen et al.[25] suggested an increased risk of suicide for the same AEDs, when indication was not restricted.

Cardiovascular medications

Two nested case-control studies [27, 28] and three cohort studies [29-31] assessed risk of suicide associated with various cardiovascular medications. In all but one, there was no evidence of association with increased or decreased suicide risk. An initial suggestion of increased risk of suicide with calcium channel blockers (CCB) was made by Lindberg et al. but the reported association was questioned due to small sample size and lack of control for confounding factors [42, 43]. Subsequent studies dismissed any association with CCB use and suicide.[27, 28, 31] Similarly, there was no difference in risk for angiotensin converting enzyme (ACE) inhibitor or β-blocker use compared to non-use [27] during monotherapy versus the general population.[31] An increased

standardised mortality ratio was, however, suggested for highly lipid soluble β-blockers but attributed in part to use in migraine.[31]

An unexpected increased suicide risk with angiotensin II receptor antagonists was reported by Callréus et al. (OR: 3.52 [95% CI 1.33-9.30]),[27] despite control of multiple potential confounding factors. However, few suicides were reported (current use n=5) and, when controlled for psychiatric history, this association became non-significant. Based on the same number of suicide cases, no association between statins and suicide was made. Corroboratively, Haukka et al.[29] suggested no increase in suicide risk in statin users versus non-users, in any follow-up time investigated. When cardiovascular medication use was compared to non-use by Voaklander et al. only diuretics were suggested to significantly influence risk; a protective effect was suggested in the fully adjusted analysis (OR 0.49 [95% CI 0.31-0.76]).[40]

Leukotriene receptor antagonists (LTRAs)

Two observational studies reported that no increased risk of suicide or attempted suicide was apparent when LTRAs, montelukast, zafrilukast and zileuton, were used for the treatment of asthma.[32, 33] No suicides were reported in Jick et al.'s cohort of individuals exposed to montelukast,[32] although one case was retrospectively disqualified based on time lag between exposure and outcome. Similarly, Schumock et al. did not detect any difference in suicide attempt during use of any LTRA compared to non-use in their nested case-control study of individuals diagnosed with asthma, aged 5-24 years.[33]

Isotretinoin

No difference in the combined risk of attempted and completed suicide was associated with isotretinoin or antibiotics, compared to non-exposure, in Jick et al.'s cohort of individuals with acne, regardless of psychiatric history.[34] Similarly, there was no significant difference in attempted suicide risk before treatment compared to six months after treatment, in Sundström et al.'s crossover analysis.[35] On the other hand, when compared to the general population, the highest elevated risk was observed in the first six months of treatment, but this risk was rising prior to medication initiation.

Corticosteroids

No difference in suicide risk was associated with steroid use versus non-use by Voaklander et al.[40] Conversely, in Fardet et al's (2012) cohort study, a five-fold increased risk of suicide and attempted suicide was

reported following glucocorticoid exposure, compared to non-exposure (HR: 5.27 [95% CI 3.82-7.29]) but incidence was low.[36] In a subsequent self-controlled case series, no difference was detected during withdrawal period compared to treatment periods,[37] although this assertion was based on only six cases.

Antibiotics

In the single nested case-control study which focused on quinolone antibiotics, no difference in risk of attempted suicide was detected following exposure to quinolones or other antibiotics, compared to non-exposure.[38]

Varenicline

One cohort study reported suicide attempt, separately from other outcomes, in relation varenicline use. There was no difference in risk during use of varenicline or nicotine replacement patches, when individuals were matched by propensity score.[39]

DISCUSSION

The primary aims of this systematic review were to establish which groups of non-psychotropic medications have been associated with suicide and attempted suicide in observational epidemiological studies; and to quantify the influence these medications have on this risk, beyond that conferred by underlying illness. Overall, the contribution of corticosteroids,[36, 40] isotretinoin [34, 35] and AEDs [22-26] to risk of suicide and attempted suicide remains unresolved whilst there seems no increased risk associated with cardiovascular medications.[27-29, 31] Neither the single studies which investigated quinolones [38] or varenicline,[39] nor the two which assessed LTRAs,[32, 33] suggested an increased risk of suicidality.

With the exception of the cardiovascular medicines, all groups of medications identified in this review have been the subject of FDA or UK Medicines and Healthcare Products Regulatory Agency (MHRA) warnings. In 2008, the FDA warned of an increased risk of suicidal behaviour and ideation during AED use, following a meta-analysis of 199 placebo-controlled RCTs involving 43,892 patients. An overall odds ratio of 1.80 (95% CI 1.24-2.66) was reported.[44] This mainly reflected an increased risk of suicidal ideation and attempted suicide because only four suicides in total were reported across almost two hundred trials. This emphasises the lack of statistical power of RCTs, and even meta-analysis of numerous trials, for examining an outcome as rare as death by suicide. Concerns were raised from medical and research communities regarding the reliability and impact of this warning. The risk was attributed as a class effect despite variation in risk associated with individual AEDs,

there was potential for heterogeneity in outcome designation and there was an unexplained differential risk dependent upon study location.[45, 46] Our review of the observational work which followed is in corroboration with Ferrer et al.'s review, which considered AEDs for any indication, that the association between dying by suicide and AEDs remains inconclusive.[15]

Varenicline is associated with the highest level of warnings issued by the FDA. It may therefore be surprising that only one study which pertains to varenicline is included in this review. This is because no other observational studies considered only suicide or attempted suicide outcomes. Neither observational studies which considered all self-harm outcomes [47, 48] nor a pooled analysis of RCTs which considered all suicidality outcomes suggested an increased risk associated with varenicline,[39] compared to other smoking cessation treatments or placebo. The FDA black-box warning continues to be challenged by the manufacturers of varenicline, based on a meta-analysis of placebo-controlled RCTs.[49] The FDA also warns of suicidal behaviour during use of isotretinoin and in 2014, an expert review in the UK could neither confirm nor discount an association of suicide with isotretinoin.[50] Isotretinoin is one of three non-psychotropic medications on the list of the top twenty medicines most frequently associated with suicide in UK spontaneous reports.[51] The other two medications, efavirenz and mefloquine,[51] carry warnings for suicidal behaviour in their drug monographs.[18] No observational studies reported suicide or attempted suicide outcomes for these medications. Warnings of psychiatric adverse events, including suicidal behaviour, exist for glucocorticoids in the UK, but this group does not feature in the list of FDA drugs linked with suicidal behaviour.[10]

This systematic review has found considerable heterogeneity amongst studies, which makes comparisons both within and between medication groups difficult and quantitative meta-analysis inappropriate. All of the studies that considered cardiovascular medications reported suicide only. Conversely, there was variation in reported outcomes within classes of other medications. Some studies reported attempted suicide or combined suicide and attempted suicide outcomes, sometimes because suicide outcomes were too rare to enable detection of differences between groups. Furthermore, different comparison groups were chosen. Schumock et al. controlled for confounding by indication and disease severity by restricting the comparator cohort to people with asthma who use controller medication.[33] On the other hand, comparator group demographics could not be stipulated when standardised mortality rates were estimated.[31]

It is imperative that the underlying risk posed by physical illness as well as pre-existing mental illness or psychological distress is recognised when interpreting any elevation in risk associated with non-psychotropic

medication. This is of particular importance for AEDs because epilepsy has been associated with a two-fold increased risk of suicide compared to the general population.[52] Furthermore, AEDs can be prescribed for a variety of physical and psychiatric conditions including bipolar disorder, which is associated with over a seventeen-fold increased risk of suicide.[7, 53] In this review, articles were excluded if the study population was defined by presence of mental illness, to aid interpretation of possible associations with medication separately from to those conferred by the mental illness. We acknowledge that a limitation of this review is that some studies allowed AED use for any indication, which may have included mental illness. This was, however, accounted for by adjustment for or stratification by mental illness in those studies.

Additionally, medications may be used for alternative indications where first line treatment has failed. This could contribute to the increased suicide risk observed by Arana et al. when AEDs were prescribed for conditions other than epilepsy, depression or bipolar disorder, much of which was suspected to be indicated for pain.[22] Similarly, Sørensen et al. attributed the increased risk associated with lipid soluble β-blockers in part to the higher prevalence of migraine in this group.[31] Glucocorticoids are often introduced during disease relapse which could contribute to suicide risk, even when indication is controlled for.[36] Likewise, the increased suicide risk identified prior to initiation of isotretinoin, could be a factor of acne severity.[35]

Observational studies are essentially useful for demonstrating associations rather than causation, although tentative inferences of causality can be put forward if there is robust evidence of concurrence with Bradford-Hill's criteria.[54] One of his seven pillars of causality is the biological plausibility of the event, in this case a postulated adverse reaction. Adverse reactions to medication can be denoted as Type A, an exaggerated effect of the pharmacology of the medication, or Type B, usually an idiosyncratic event, often detected in post-marketing surveillance.[55] Any observed elevation in risk of suicide could be a consequence of induced depression or occur independently. Potential pathways to suicidality have been suggested for some, but not all, medicines included in this review. Interference with γ-aminobutyric acid (GABA) and glutamate may contribute to any observed link between AED usage and elevated suicide risk,[56] but would differ between individual AEDs. Increased cortisol levels have also been linked to suicide.[57] Therefore exogenously introduced glucocorticoids could confer similar effects. Reduced lipid levels have also been associated with increased suicide risk.[5] Conversely, the included studies do not suggest increased risk with lipid-lowering medication use,[27, 29], corroborative with earlier work by Yang et al.[58]

To our knowledge, this is the first systematic review to consider the impact of non-psychotropic medication use on risk of suicide and attempted suicide. Only suicide and attempted suicide outcomes were considered, to minimise outcome misclassification possible when other suicidality outcomes are used as proxies.[11, 13] Determination of an individuals' intent to die by suicide is challenging [59, 60] therefore other terminologies may incorporate suicide attempt. For example, 'non-fatal self-harm' represents a continuum of suicidal and self-harm behaviours with varying motivations and intentions. To avoid overestimation of outcomes, studies were included only if authors explicitly used the label 'suicide attempt'. This may have precluded inclusion of studies which reported attempted suicide as a composite outcome within another definition of suicidality, and is therefore a limitation of our review. We also acknowledge that screening of studies by a single author introduced the potential for selection bias. In an attempt to reduce this bias, other authors were consulted if selection was unclear and included records were hand-searched for suitable studies, which served as a cross-check.

Inclusion of studies from any country introduced further variation in suicide classification.[61] In the UK, open verdicts are conventionally included in epidemiological suicide definitions, as most are deemed to be probable suicides that were not designated as such due to the high burden of proof required in coroners' courts.[62] In other countries, including the United States, open verdicts are generally not included in suicide case definitions. For example, Patorno et al. separately reported violent deaths in their US population, up to 87% of which may be suicides. The trends identified were however similar to those for suicide and attempted suicide outcomes.[26]

Determining the cause of any observed increased risk, specifically as a result of mental or physical illness, the medication itself, or a combination of factors, represents a major challenge. Overall assessments are difficult to report due to variation between study outcomes, populations and control for psychiatric and physical comorbidities. Robust identification of suicidality outcomes and control of comorbidities is needed in future observational studies, particularly to investigate suicide risk in association with AEDs, isotretinoin and corticosteroids.

CONTRIBUTORSHIP STATEMENT

HG was involved in study design, screened all studies, summarised and interpreted studies and drafted the manuscript.

RW was involved in study design, interpretation of studies, reviewed and edited versions of the manuscript.

NK was involved in study design and reviewed and commented on versions of the manuscript.

DA was involved in study design, interpretation of studies, reviewed and edited versions of the manuscript.

COMPETING INTERESTS

None

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DATA SHARING AGREEMENT

No additional data are available but details of included studies are available from the corresponding references.

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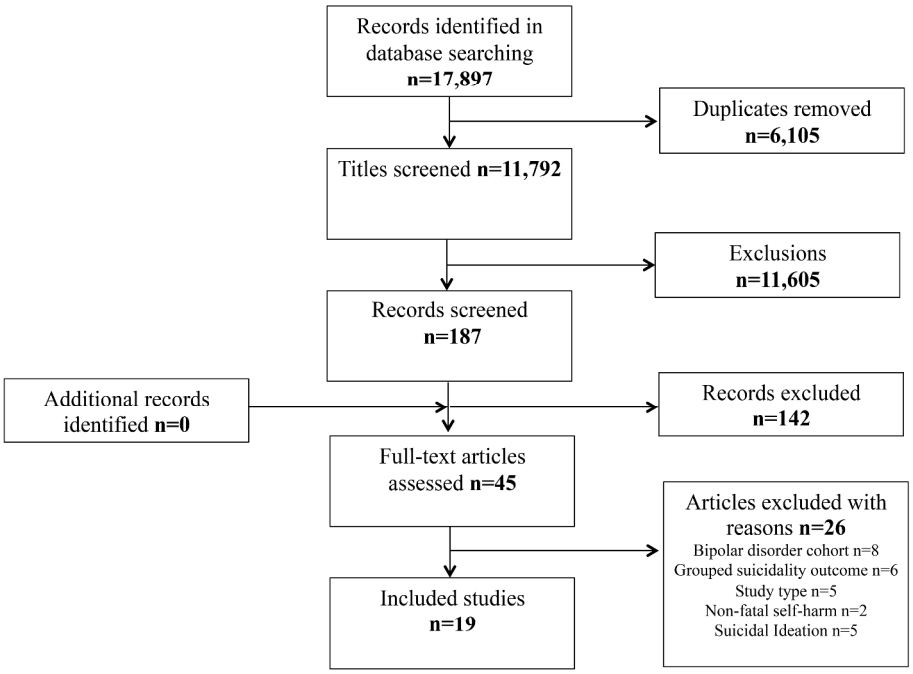

Fig. i Flow Diagram of Included Studies
508x381mm (300 x 300 DPI)

Non-psychotropic Medication and Risk of Suicide or Attempted Suicide: a Systematic Review

Supplementary Material: Study Protocol

a) Rationale: To assess postulated associations between non-psychotropic medications and suicide risk (increase, decrease or no difference in risk) compared to non-use or use of an alternative medication. Non-psychotropic medication is defined as any medication which does not primarily treat the mental illnesses listed in Diagnostic and Statistics Manual V, and operationally defined by BNF category exclusion of sections 4.1-4.3, [1] 4.4, 4.10.1, 4.10.3 and 4.11.

b) Objectives:

1. To perform a systematic literature search to identify which non-psychotropic medications have been examined, and what associations have been reported, in relation to risk of attempted and completed suicide in observational, epidemiological studies.

2. To identify reported associations for each drug group to understand the extent to which studies corroborate or disagree, taking into consideration heterogeneity between studies.

3. To critically evaluate the strengths and limitations of the included studies.

c) Protocol: This protocol was produce in line with PRISMA guidance, but adapted for observational studies.

d) Eligibility Criteria:

i) Population:

- Exposure to any non-psychotropic drug
- Any country: variability in suicide reporting exists between countries and is a limitation when comparing outcomes

Exclusion Criteria:

- Studies entirely in cohorts with mental illness
- Medication as method for overdose
- Illegal or recreational drug use (including alcohol)

ii) Outcome:

- Attempted and/or completed suicide-as defined by the study authors

Exclusion Criteria:

- Suicidal Ideation
- Other outcomes of suicidality where suicide and/or attempted suicide were not separately analysed
-

iii) Study Design:

- Observational design: cohort, case control, nested case control, case-crossover analysis

Exclusion Criteria:

- Randomised Control Trials-unpowered to detect such rare outcomes
- Cross-sectional studies
- Case reports and case series
- Spontaneous reporting systems

v) Year:

- Reports published since 1990- to present. Encompasses inception of large electronic healthcare databases. Provides a reasonable time scale following heightened awareness in 1990, through the infamous case series published by Teicher et al. regarding antidepressants. [2] Study period not stipulated.

vi) Language:

- English

e) Information Sources:

Four databases independently searched with variation in 'medical subject headings' (MESH) and search terms, to account for variation in speciality: *Embase, PsycINFO, Medline and International Pharmaceutical Abstracts.*

Exclusion Criteria:

- Conference abstracts – due to insufficient information
- Grey literature eg. PhD thesis' were not searched

f) Search Strategy:

Search terms were tailored to each database and medical subject headings (MeSH) and explode features were used as appropriate. The initial search in each database was general to encompass any medication, and followed by narrower searches pertaining to medication identified in the initial search.

1. Embase

a) Initial Search

suicide OR suicidal (ti.ab.) AND medicine (ti. ab.) OR medicat* (ti. ab.) OR drug therapy (exp., ti.ab.)

b) Antiepileptics

suicide or suicidal (ti.ab.) AND anticonvulsive agent (exp.)

c) Calcium Channel Blockers and β-blockers

suicide OR suicidal (ti.ab.) AND calcium channel blocking agents (exp) OR beta adrenergic receptor blocking agent (exp)

d) Lipid Lowering Drugs

suicide OR suicidal (ti.ab.) AND hydroxymethylglutaryl coenzyme A reductase inhibitor AND atorvastatin (ti.ab.) OR rosuvastatin (ti.ab.) OR pravastatin (ti.ab.) OR fluvastatin (ti.ab.) OR simvastatin (ti.ab.) OR colesevelam (ti.ab.) OR colestyramine (ti.ab.) OR cholestyramine (ti.ab.) OR colestipol (ti.ab.) OR ezetimbe (ti.ab.) OR bezafibrate (ti.ab.) OR ciprofibrate (ti.ab.) OR fenofibrate (ti.ab.) OR gemfibrozil (ti.ab.) OR hypocholesterolemic agent (exp.)

e) Smoking cessation medication

suicide or suicidal (ti.ab.) AND varenicline (exp) OR amfebutamone (exp) OR *smoking cessation

f) Leukotriene Receptor Antagonists

suicide OR suicidal (ti.ab.) AND Leukotriene Antagonists (exp.) AND montelukast (ti.ab.) OR zafrilukast (ti.ab.) OR zileuton (ti.ab.)

g) Glucocorticoid

suicide OR suicidal (ti.ab.) AND glucocorticoid (exp.)

h) Quinolone

suicide OR suicidal (ti.ab.) AND quinolone derivative (exp.)

i) Isotretinoin

suicide OR suicidal (ti.ab.) AND isotretinoin (exp.)

2. Medline

a) Initial Search

suicide OR suicidal (ti.ab.) AND medicat$ (ti.ab.) OR prescriptions/(MeSH) OR *drug prescriptions/(MeSH) OR Pharmaceutical Preparations (exp.)

b) Antiepileptics

suicide OR suicidal (ti.ab.) AND antiepileptic$ (ti.ab.) OR Anticonvulsants (exp.)

c) Calcium Channel Blockers or β-blockers

suicide OR suicidal (ti.ab.) AND Calcium Channel Blockers (exp.) OR Adrenergic beta-Antagonists (exp.)

d) Lipid Lowering Drugs

suicide OR suicidal (ti.ab.) AND anticholesteremic agents (exp.) OR hydroxymethylglutaryl-coareductase inhibitors (exp.) OR colesevelam (ti.ab) OR colestyramine (ti.ab.) OR cholestyramine (ti.ab.) OR colestipol (ti.ab.) OR ezetimbe (ti.ab.) OR bezafibrate (ti.ab.) OR ciprofibrate (ti.ab.) OR fenofibrate (ti.ab.) OR gemfibrozil (ti.ab.)

e) Smoking cessation medication

suicide OR suicidal (ti.ab.) AND bupropion (ti.ab.) OR amfebutamone (ti.ab.) OR bupropion (exp.) OR *Smoking Cessation (MeSH)

f) Leukotriene Receptor Antagonists

suicide OR suicidal (ti.ab.) AND leukotriene receptor blocking agent (exp.) OR montelukast (ti.ab.) OR zafrilukast (ti.ab.) OR zileuton (ti.ab.)

g) Glucocorticoids

suicide OR suicidal (ti.ab.) OR glucocorticoids (exp) OR budenoside (ti.ab.) OR hydrocortisone (ti.ab.) OR prednisolone (ti.ab.) OR prednisone (ti.ab.) OR betamethasone (ti.ab.) OR deflazacort (ti.ab.) OR dexamethasone (ti.ab.) OR methylprednisolone (ti.ab.) OR triamcinolone (ti.ab.)

h) Quinolones

suicide OR suicidal (ti.ab.) AND quinolones (exp) OR fluoroquinolones (exp) OR ciprofloxacin (ti.ab) OR norfloxacin (ti.ab.) OR ofloxacin (ti.ab.) OR nalidixic acid (ti.ab) OR levofloxacin (ti.ab.) OR moxifloxacin (ti.ab.) OR enoxacin (ti.ab.) OR acrosaxcin (ti.ab.) OR temafloxacin (ti.ab.)

i) Isotretinoin

suicide OR suicidal (ti.ab.) AND isotretinoin (exp) OR 13-cis retinoic acid (ti.ab.) OR accutane (ti.ab) OR roaccutane (ti.ab.)

3. PsycInfo

a) Initial Search

suicide OR suicidal (ti.ab.) AND medicat$ (ti.ab.) OR medicine (ti.ab.) OR drug$ (ti.ab.)

b) Antiepileptics

suicide OR suicidal (ti.ab.) AND *anticonvulsive drugs (MeSH) OR carbamazepine (ti.ab) OR eslicarbazepine (ti.ab) OR oxcarbazepine (ti.ab) OR ethosuxamide (ti.ab) OR gabapentin (ti.ab) OR pregabalin (ti.ab) OR lacosamide (ti.ab) OR lamotrigine (ti.ab) OR levetiracetam (ti.ab) OR perampanel (ti.ab) OR phenobarbit$ (ti.ab) OR primidone (ti.ab) OR phenytoin (ti.ab) OR retigabine (ti.ab) OR rufinamide (ti.ab) OR tiagabine

(ti.ab) OR topiramate (ti.ab) OR valproate (ti.ab) OR "valproic acid" (ti.ab) OR divalproex (ti.ab) OR vigabatrin (ti.ab) OR zonisamide (ti.ab) OR clobazam (ti.ab) OR clonazepam (ti.ab)

c) Calcium Channel Blockers or β-blockers

suicide OR suicidal (ti.ab.) AND amlodipine (ti.ab) OR diltiazem (ti.ab.) OR isradipine(ti.ab) OR lacidipine(ti.ab) OR lercanidipine (ti.ab) OR nicardipine (ti.ab) OR nifedipine (ti.ab) OR nimodipine (ti.ab) OR verapamil (ti.ab) OR propranolol (ti.ab) OR acebutolol (ti.ab) OR atenolol (ti.ab) OR bisoprolol (ti.ab) OR carvedilol (ti.ab) OR celiprolol (ti.ab) OR esmolol (ti.ab) OR labetaol (ti.ab) OR metoprolol (ti.ab) OR nadolol (ti.ab) OR nebivolol (ti.ab) OR oxprenolol (ti.ab) OR pindolol (ti.ab) OR sotalol (ti.ab) OR timolol (ti.ab)

d) Lipid Lowering Drugs

suicide OR suicidal (ti.ab) AND statins (exp) OR atorvastatin (ti.a.b) OR rosuvastatin (ti.ab.) OR pravastatin (ti.ab) OR fluvastatin (ti.ab.) simvastatin (ti.ab.) OR colesevelam (ti.ab.) OR colestyramine (ti.ab.) OR cholestyramine (ti.ab.) OR colestipol (ti.ab) OR ezetimbe (ti.ab.) OR bezafibrate (ti.ab.) OR ciprofibrate (ti.ab.) OR fenofibrate (ti.ab.) OR gemfibrozil (ti.ab.)

e) Smoking Cessation

suicide OR suicidal (ti.ab) AND *smoking cessation (MeSH) OR varenicline (ti.ab.)

f) Leukotriene Receptor Antagonists

suicide OR suicidal (ti.ab) AND leukotriene receptor antagonist$ (ti.ab.) OR leukotriene receptor blocker$ OR montelukast (ti.ab.) OR zafrilukast (ti.ab.) OR zileuton (ti.ab.)

g) Quinolone

suicide OR suicidal (ti.ab) AND antibiotics (exp)

h) Glucocorticoids

suicide OR suicidal (ti.ab) AND glucocorticoids (exp) OR budesonide (ti.ab.) OR hydrocortisone (ti.ab.) OR prednisolone (ti.ab.) OR prednisone (ti.ab) OR betamethasone (ti.ab) OR deflazacort (ti.ab) OR dexamethasone (ti.ab) OR methylprednisolone (ti.ab) OR triamcinolone (ti.ab.)

i) Isotretinoin

suicide OR suicidal (ti.ab) AND isotretionon (ti.ab) OR "13-cis retinoic acid" (ti.ab) OR accutane (ti.ab) OR roaccutane (ti.ab)

4. International Pharmaceutical abstracts

a) Initial Search

suicide OR suicidal (ti.ab) AND durg$ (ti.ab.) OR prescription$ (ti.ab.) OR medicine (ti. ab) OR medicat$ (ti.ab.)

b) Antiepileptics

suicide OR suicidal (ti.ab) AND anticonvulsant$ (ti.ab.) OR antiepileptic$ (ti.ab) OR carbamazepine (ti.ab) OR eslicarbazepine (ti.ab) OR oxcarbazepine (ti.ab) OR ethosuxamide (ti.ab) OR gabapentin (ti.ab) OR pregabalin (ti.ab) OR lacosamide (ti.ab) OR lamotrigine (ti.ab) OR levetiracetam (ti.ab) OR perampanel (ti.ab) OR phenobarbit$ (ti.ab) OR primidone (ti.ab) OR phenytoin (ti.ab) OR retigabine (ti.ab) OR rufinamide (ti.ab) OR tiagabine (ti.ab) OR topiramate (ti.ab) OR valproate (ti.ab) OR "valproic acid" OR divalproex (ti.ab) OR vigabatrin (ti.ab) OR zonisamide (ti.ab) OR clobazam (ti.ab) OR clonazepam (ti.ab)

c) Calcium Channel Blockers and β-blockers

suicide OR suicidal (ti.ab) AND amlodipine (ti.ab) OR diltiazem (ti.ab) OR isradipine (ti.ab) OR lacidipine (ti.ab) OR lercanidipine (ti.ab) OR nicardipine (ti.ab) OR nifedipine (ti.ab) OR nimodipine (ti.ab) OR verapamil (ti.ab) OR propranolol (ti.ab) OR acebutolol (ti.ab) OR atenolol (ti.ab) OR bisoprolol (ti.ab) OR carvedilol (ti.ab) OR celiprolol (ti.ab) OR esmolol (ti.ab) OR labetalol (ti.ab) OR metoprolol (ti.ab) OR nadolol (ti.ab) OR nebivolol (ti.ab) OR oxprenolol (ti.ab) OR pindolol (ti.ab) OR sotalol (ti.ab) OR timolol (ti.ab) OR "calcium channel blocker$" (ti.ab) OR "beta-blocker$" (ti.ab) OR "beta adrenoreceptor antagonist" (ti.ab)

d) Lipid Lowering Drugs

suicide OR suicidal (ti.ab) AND atorvastatin (ti.ab) OR rosuvastatin (ti.ab) OR pravastatin (ti.ab) OR fluvastatin (ti.ab) OR simvastatin (ti.ab) OR colesevelam (ti.ab) OR colestyramine (ti.ab) OR cholestyramine (ti.ab) OR colestipol (ti.ab) OR ezetimbe (ti.ab) OR bezafibrate (ti.ab) OR ciprofibrate (ti.ab) OR fenofibrate (ti.ab) OR gemfibrozil OR "lipid lowering drugs" (ti.ab)

e)Smoking cessation

suicide OR suicidal (ti.ab) AND varenicline (ti.ab) OR smoking cessation (ti.ab)

f) Leukotriene Receptor Antagonists

suicide OR suicidal (ti.ab) AND "leukotriene receptor antagonist$" (ti.ab) OR "leukotriene receptor blocker$" (ti.ab) OR montelukast (ti.ab) OR zafrilukast (ti.ab) OR zileuton (ti.ab)

g) Quinolones

suicide OR suicidal (ti.ab) AND quinolone$ (ti.ab) OR fluroquinolone$ (ti.ab) OR ciprofloxacin (ti.ab) OR norfloxacin (ti.ab) OR ofloxacin (ti.ab) OR nalidixic acid (ti.ab) OR levofloxacin (ti.ab) OR moxifloxacin (ti.ab) OR enoxazin (ti.ab) OR acrosoxacin (ti.ab) OR temafloxacin (ti.ab)

h) Glucocorticoid

suicide OR suicidal (ti.ab) AND glucocorticoid$ (ti.ab) OR budesonide (ti.ab) OR hydrocortisone (ti.ab) OR prednisolone (ti.ab) OR prednisone (ti.ab) OR betamethasone (ti.ab) OR deflazacort (ti.ab) OR dexamethasone (ti.ab) OR methylprednisolone (ti.ab) OR triamcinolone (ti.ab)

i) Isotrentioin

suicide OR suicidal (ti.ab) AND isotretinoin (ti.ab) OR "13-cis retinoic acid" (ti.ab) OR accutane (ti.ab) OR roaccutane (ti.ab)

g) Data Extraction: Independently (one investigator, HCG) with discussion with DMA, RTW and NK when decision to include or exclude was unclear.

h) Data Items: List of variables for which data were sought: medication, suicide, suicide attempts, comparator, suicide risk, confounder adjustments

i) Risk of Bias in Individual Studies: Drug exposure classification, outcome definition, population, database suitability, confounding factor adjustment, baseline characteristics. The quality assessment framework proposed by Neyarapally et al. was used to guide assessment of study quality.[3]

j) Summary measures: Not specified but include odds ratio, hazard ratio, incidence rate ratio, risk ratio, standardised mortality rate, relative risk

k) Risk of bias across studies: One author assessed all studies and discussed at length with co-authors where decision to include was unclear. Critical appraisal was discussed at length with co-authors.

References

1. Gunnell D, Irvine D, Wise L, et al. Varenicline and suicidal behaviour: a cohort study based on data from the General Practice Research Database. BMJ 2009;339:b3805
2. Teicher MH, Glod C, Cole JO. Emergence of intense suicidal preoccupation during fluoxetine treatment. Am J Psychiatry 1990;147(2):207-10
3. Neyarapally GA, Hammad TA, Pinheiro SP et al. Review of quality assessment tools for the evaluation of pharmacoepidemiological safety studies. BMJ Open 2012;2(5) doi: 10.1136/bmjopen-2012-001362

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	x
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4 and online supplementary material. No interventions specified as RCTs not considered. Open to any comparator in order to address the primary research aims
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Online supplementary material
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4 but nature of research questions warrants relatively unrestrictive criteria
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4 (and online supplementary material
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5. Relevant results which expressed risk of suicide with non-psychotropic medication were

PRISMA 2009 Checklist

			accepted, no specific format was stipulated.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4 and defined in *Table i*
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5. The primary focus was to establish *which* non-psychotropic medications have been associated with suicide. Bias was assessed in the critique *(Table i*) rather than precluding inclusion.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4 lists examples but is non-exhaustive. This was to avoid restriction of how risk was presented.
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	n/a, meta-analysis inappropriate for this research question

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4– selective reporting in studies attempted to be circumvented by personal contact with authors
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	*Fig. 1*
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	*7-9, Table i*
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	*7-9, Table i*

PRISMA 2009 Checklist

Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	*7-9, Table i*
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	*7-9, Table i*
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12, 15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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