Title: Cardiovascular and metabolic Side Effects in Patients Using Anti-depressants or Antipsychotic Medications: A Systematic Review Protocol.

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1 BACKGROUND:

1.1 MORTALITY BURDEN AND PHYSICAL COMORBIDITIES AMONG PEOPLE WITH MENTAL HEALTH CONDITIONS:

According to the world health organization (WHO), mental health conditions are defined as set of diseases that are mainly characterized by abnormalities in thought, behaviour and emotion in a way that may hinder their effective interaction with other people (1). Furthermore, mental health conditions are clinically diagnosable disorders that may sustain for long period or demonstrate recurrent pattern during the life. Mental health conditions are considered universal disorders that affect people at wide range regardless their age and geographical location (2,3). Around of 50% mental health condition including schizophrenia are most likely diagnosable by the age of 14 and years old age. People with major mental health conditions such as schizophrenia and depression experience around 40 to 60 % higher chances of premature death compared to the general population(1).

Cardiovascular diseases have been reported to be a major cause of death in patients with mental health conditions (4,5). Patients with schizophrenia show an increased rate of mortality due to cardiovascular diseases (13). The aetiology of cardiovascular complications in people with mental health conditions is multidimensional in nature, which includes several aspects such as life style factors, genetic factors and cardiovascular related diseases. The high mortality that are observed in this population was suspected to be linked to the increased rate modifiable cardiovascular risk factors (5). Prevalence studies indicate that modifiable cardiovascular risk factors such as diabetes, abnormal lipid profile, glycemic abnormalities, weight gain, serious alterations in the cardiac-conductivity (6), hypertension and insulin resistance , are highly prevalent in patients with psychotic illness such as schizophrenia and depression (5,7). Although, the exact underlining cause of cardiovascular complications in patients with mental conditions is not well defined (5), there is a growing body of evidence which have addressed the possible association between the use of antipsychotics, antidepressants and the increased incidence of cardiovascular disease (CVD) in people using these medications. However, the majority of previous work addressed several confounding factors other than the effect of the targeted psychotropic drugs for example life style and genetic factors. This makes difficult to build a conclusive estimation of the actual impact of antipsychotics and antidepressants on the prevalence of CVDs.

1.2 ANTIPSYCHOTIC AND ANTIDEPRESSANTS AS INDEPENDENT RISK FACTORS FOR CARDIOVASCULAR AND METABOLIC COMORBIDITIES IN PEOPLE WITH MENTAL HEALTH CONDITIONS:

One particular interest to researchers and clinicians is the increased risk of cardiovascular complications (CVCs) and their associated risk factors with the use of psychotropic medications. Evidence provided by Wu CS et al (6) and others (7) through the results of the review that was done to evaluate the cardiometabolic characteristics for individual psychotropic classes, which revealed that antipsychotic drugs and other psychotropic agents such as antidepressants have the potential to causes cardiovascular risk factors or accelerate pre-existing ones. The adverse effects on the cardiovascular system can be caused by different mechanisms which are beyond the focus of this section, however, this effect can be caused either by direct action on the heart or through indirect cascade of metabolic dysregulations which can finally lead to adverse cardiac events (8).

Antipsychotic medications are widely used in the management of schizophrenia and other mental health conditions. Antipsychotic drugs are classified into two major classes. The first class is known as typical antipsychotics or first generation antipsychotic drugs (FGAs). This group is characterized by their effectiveness in relieving positive psychotic symptoms of schizophrenia such as hallucinations. However, they have been proved to be less effective against negative symptoms, which lead to the development of the new generation of antipsychotic drugs which are known as second generation antipsychotic or atypical antipsychotic drugs (9). Second generation antipsychotic drugs are more effective than typical antipsychotic drugs in relieving negative symptoms, so the compliance to therapy would increase hence decrease frequency of relapse (10)

Antidepressants on the other hand, are considered a typical intervention to manage people who suffer from depressive mood disorders and other psychotic disorders such as depressive schizophrenia. In the future, it is estimated that mortality due to cardiovascular diseases along with depressive diseases will be escalated globally (11,12). Moreover, some studies revealed that depressive disorders tend to be associated with more prevalence of cardiovascular risks (13).

1.2.1 Antipsychotic medications:

At normal therapeutic dose first generation antipsychotic drugs (FGAs) have been known to cause motor abnormalities mainly extrapyramidal symptoms (EPS) (9,10). Second generation antipsychotic drugs, on the other hand, have less motor side effects compared to the previous generation. Moreover, the extrapyramidal symptoms (EPS) caused by second generation antipsychotic drugs (SGAs) tend to be dose dependent with achievable therapeutic effect that is free of extrapyramidal symptoms (EPS), which makes second generation antipsychotic drugs (SGAs) more preferable over the first generation antipsychotic drugs (FGAs) (10). However, second generation antipsychotic drugs have similar cardiovascular risks that represented in their negative effects on the cardiac conductivity, vascular changes and metabolic homeostasis.

1.2.1.1 Cardiovascular side effects of antipsychotic drugs:

Antipsychotic drugs are known to cause cardiac arrhythmia as well as orthostatic hypotension (18). In healthy population, the QTc interval ranges from 380 to 450 milliseconds (ms) and this can vary according to patients' age and gender. QT prolongation can be defined as > 450 to 460 ms increase above the normal physiologic range (14). Both generations of antipsychotics have the capability to cause electrocardiogram (ECG) changes (14). Epidemiologic studies (6,15) correlate this lengthen in QTc interval with the increased risks of sudden death that have been reported among patients using antipsychotic drugs. Antipsychotic drugs associated with this risk include but are not limited to haloperidol, olanzapine, quetiapine, risperidone and sulpiride (6). The arrhythmogenis effect caused by antipsychotic was reported with high doses of antipsychotic drugs, however, this effect can occur at normal therapeutic doses. Therefore, determining the need for regular ECG monitoring can be challenging. Furthermore, antipsychotic drugs have been reported to cause changes in blood pressure. Orthostatic hypotension is the most frequent vascular effect of antipsychotic drugs. Up to 40% of patients treated with antipsychotic reported to suffer from sudden drop of blood pressure at standing. Orthostatic hypotension can be defined either as ≥20 mmHg reduction in systolic blood pressure (SPB) or ≥10mm Hg decrease in diastolic blood pressure (DBP) after standing for 3 minutes (16). Notably, the hypotensive effect tend to occur at the early phase of psychotic treatment (16), however, it is not clear wither this effect is dose dependent knowing that loading dose regiment is commonly utilised at the early stages of psychotic treatment. Besides, the orthostatic hypotensive effect have been proved to be common among elderly patients treated with antipsychotic therapy and orthostatic hypotension is general concern in old patients treated with antipsychotic drugs as risks of falls would be magnified.

1.2.1.2 Metabolic side effects of antipsychotic drugs:

Weight gain is a major components of the metabolic dysregulations that caused by antipsychotic drugs (7,9) and its considered a major risk factor for cardiovascular diseases (CVDs). The effect of weight gain can vary among different antipsychotic classes (7,9), since it was more frequent with SGAs. Moreover, there is a hierarchical effect on the risks of weight gain among antipsychotics drugs, that has been confirmed by different studies (7,9,17). Several clinical studies () showed that second generation antipsychotic drugs (SGAs) primarily clozapine and olanzapine demonstrate greater weight inducing effects compared to other antipsychotic drugs (15), in addition to other lipid associated risk factors such as dyslipidemias and insulin resistance. Some studies highlighted that specific patients characteristics such as age and degree of exposure to antipsychotic drugs may increase risks of weight gain (9). Young patients have been reported to be the most susceptible to metabolic dysregulations including weight gain. This is highly important when considering the fact that some mental health conditions such as schizophrenia and depression tend to develop at young age and may continue to progress in later life (18), and the antipsychotic induced weight effect have been suggested to be persistence and even be cumulative(19). This may indicate warning signs of increased risks of cardiovascular disorders due to obesity at early stages of life.

Other metabolic dysregulations have been associated with the use of antipsychotic drugs such as dyslipidemias, which apparently associates with the body weight. Second generation antipsychotics mostly clozapine and olanzapine have been associated with the higher tendency to cause dyslipidemias mainly hyperlipidemia and hypertriglyceridemia (7).Hypertriglyceridemia induced by antipsychotics can be developed rapidly as the level of triglyceride (TG) can be doubled within two weeks after initiating the treatment with antipsychotics (7). Consequently, antipsychotic drugs have been reported to cause metabolic syndrome (MS). A cluster of abnormalities that associate with metabolic disturbances including central obesity, dyslipidemias, plasma glucose abnormalities, and hypertension (20). Results from a prevalence study (21), reported a considerable increase in rate of metabolic syndrome among patients treated with antipsychotic drugs, as 40.2% of the participants were diagnosed to have metabolic syndrome. Some metabolic criteria that identify patients with metabolic syndrome (MS) have been previously addressed to be associated with the use of antipsychotic drugs and hence the increased risk for cardiovascular diseases and other metabolic conditions such as diabetes mullets (DM). Moreover, patients with metabolic syndrome (MS) have been reported to have high risks of developing cardiovascular and metabolic diseases such as coronary heart diseases and diabetes.

1.2.2 Antidepressants medications:

The exact pathophysiology between the cardiovascular events and depression still not well established. Amongst the suggested explanations is the potential role cardiovascular side effects of antidepressants that may adversely affect the outcomes of people suffering from cardiovascular disease (22). Several studies showed an accelerated rate of cardiac mortality among antidepressants users.

1.2.2.1 Cardiovascular side effects of antidepressants

With regard to the safety of antidepressants drugs, previous work that addressed the safety of antidepressants in people with cardiac diseases, highlighted the indirect role of antidepressants on reducing the cardiovascular risks by improving the depressive symptoms. For example, (28), selective serotonin reuptake inhibitors (SSRIs) class were mainly investigated according to their effectiveness in improving the cognitive symptoms in patients with depression and hence the general outcome on their health would improve accordingly. Certain classes of antidepressants primarily tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) have been well

established for their tendency to negatively affect the cardiac conductivity which can lead to fatal arrhythmias (11,23). Additionally, the arrhythmogenic side effect of antidepressant drugs revealed to be dose dependent (24) who reviewed the causes of cardiovascular incidents form that can result from non-cardiac drugs. Hypertension was also reported with antidepressant drugs (7). In meta-analysis study of the cardiovascular adverse effects of psychotropic drugs, antidepressants such as venlafaxine and imipramine significantly increased the diastolic blood pressure (DBP) by 1.2mmHg and 1mmHg respectively (25).

1.2.2.2 Metabolic side effects of antidepressants:

Notably, the majority of the available data regarding the metabolic effects of antidepressants focus on their effects on the weight, however controversy exist regarding the effects of antidepressants on weight gain. Some authors suggest that the increase in weight might result from the improvement of depression symptoms as a result of the improved appetite of the patient. However, others argued this view by claiming that weight gain can be a cumulative effect of antidepressant treatment since it tends to be common during the acute phase of treatment and may continue after treatment cessation (7). With respect to antidepressant drug classes, older classes such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MOAIs) have been reported to have cause weight gain more than other antidepressants classes (26). Results from meta-analysis to investigate the risks of weight gain associated with different antidepressant drugs, showed significant increase in weight from the baseline that range from 1.5kg, 1.7kg and 2kg caused by amitriptyline, mirtazapine and nortriptyline respectively over a 4–12-week period(27).

Newer antidepressant classes were also associated with substantial effect on weight. Recent review that highlights the rate of significant weight gain and factors associated with weight gain among antidepressants treated patients, pointed out that mainly paroxetine and citalopram were associated with significant weight gain, while other newer antidepressants classes may be considered to have neutral effect (28). Notably, the weight gain induced by antidepressant drugs has been reported to be associated with the duration of treatment, since this effect tends to be heighted with the increase duration of treatment. Long phase trials (16–46 weeks)(29) that compared the weight changes among patients treated with nefazodone (n=523) and selective serotonin reuptake inhibitors (SSRIs) (fluoxetine, paroxetine, and sertraline; N = 513), demonstrate that around 8.3% of patients treated with nefazodone and 17% of patients treated with selective serotonin reuptake inhibitors (SSRIs) experienced more than 7kg increased in weight. This may indicate that the weight inducing effect of antidepressants can be cumulative. However, it is not clear wither the weight inducing effects of antidepressant drugs can be reversed after ceasing the antidepressant treatment.

In addition, antidepressants have been reported to cause glucose dysregulations, major components of metabolic syndrome. In general, tricyclic antidepressants (TCAs) are the main class that reported to be associated with hyperglycaemic activities (7). Limited data are available regarding the effect of antidepressant drug on other metabolic abnormalities such as dyslipidaemias (7) and insulin sensitivity, regardless the strong evidence that was provided by the study that investigated the predictors for development of metabolic syndrome among depressive patients, which shows significant association between the use of antidepressants mainly tricyclic antidepressants (TCAs) and the risks for development of certain components of metabolic syndrome (MS) particularly dyslipedima and hypertension (95% CI, OR; 1.8 to 2.57), consequently increased risks of metabolic syndrome (MS)(30).

1.2.3 Clinical implications:

Recent review of the cardio metabolic side effects of psychotropic drugs showed a considerable variation in the metabolic effects among the different psychotropic drug classes. Currently, a head to head comparison between cardiovascular and metabolic side effects causes by different psychotropic medications (i.e. both antipsychotics and antidepressants in this context) is lacking. According to the review, the weight inducing effects that caused by antidepressants is considered lower than the effect induced by antipsychotics. For example, antidepressants tend to cause a relatively low increase in body weight, around 1.5-2 kg over 4 to 12 weeks period. In the contrary, the weight inducing effect of antipsychotic drugs was higher than the effect produced by antidepressants as they were reported to cause more than 7 kg raise in weight from the baseline after only 4 weeks treatment period (31). Regarding this difference it is essential to appreciate that the utilisation of co-treatment regimen with antipsychotic and antidepressants is a common practice in mental health (32), which can result in substantial underestimation of the synergism effect that can result from this combination.

In practice, when considering treatment with antipsychotic drugs, the use of single agent antipsychotic is more preferred over the use of combined antipsychotic therapy (33). However, resistance to antipsychotic treatment is a common problem among patients treated with antipsychotics. According to the National Institute of Health and Care Excellency (NICE) (34), atypical antipsychotic drugs mainly clozapine is preferred when response to first line antipsychotic therapy is lacking. By outweighing the risks of using drug with significant cardiovascular effects against the benefits of having better symptoms control, measures to reduce the adverse effects of the drug can be applied. As previously mentioned, combination therapy with antipsychotic drugs is not preferable, however, large proportion of patients with mental health conditions are treated with more than one antipsychotic drugs (15) Antipsychotic can be used in combinations with other psychotropic drugs for example antidepressants. Since psychotic symptoms can be manifested as depression, antidepressants can be considered to alleviate the depressive symptoms and improve the overall clinical outcome. Paradoxically, most preclinical and clinical trials on cardiovascular side effects of antipsychotic drugs and their associated risk factors focus on the effects of exposure to a single psychotropic agent.

Antidepressant drugs on the other hand, are considered mainly in patients experiencing moderate to severe depressive symptoms (26). Furthermore, tricyclic antidepressants (TCAs) are not considered a first line option in the treatment of depression (35) since the introduction of the newer antidepressant classes such as selective serotonin re-uptake inhibitors (SSRIs). Owing to their effectiveness in improving depressive symptoms along with their relatively safe cardiac profile. This was supported by the results of a meta-analysis that shown that selective serotonin reuptake inhibitors (SSRIs) have significantly lowered the level of depressive symptoms compared to the placebo. Similar results were found by number of trials that studied the efficacy of selective serotonin reuptake inhibitors (SSRIs) on relieving depressive symptoms although significance was a major issue in these studies (36). However, the use of other antidepressant classes for example tricyclic antidepressants (TCAs) remain a considerable option when response to the first line class (SSRIs) is lacking. Recent advances in management of depression (32), support the use of augmented therapy with antipsychotic drugs in the management of refractory depressive episodes. As shown by the results of the meta-analysis that investigated the effectiveness of combined therapy of

antidepressants and antipsychotic in treating patients with depression, augmented therapy with antipsychotic was superior to treatment with conventional antidepressants mono-therapy (32).

1.3 CURRENT PRACTICES IN MANAGING CARDIOVASCULAR CO-MORBIDITIES ASSOCIATED WITH ANTIPSYCHOTICS AND ANTIDEPRESSANT DRUGS:

As suggested by many studies(37,38) early intervention is crucial to compensate cardiovascular complications that can be induced by antipsychotic drugs. Previously, there was no clinical guidance for health care providers that assist clinical monitoring of cardiovascular or metabolic side effects of psychotropic drugs. Consequently, prescribers relied mainly on their knowledge along with their professional experience. Based on the results from The Clinical Antipsychotic Trials of Intervention Effectiveness CATIE (21), the European Psychiatric Association (EPA)(5) in collaboration with the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC) have published a statement which aims to improve physical health care for mentally ill people. The intention was to support the need for regular monitoring and screening of cardiovascular diseases and their risk factors among people taking antipsychotics and antidepressants (5).

In order to maximise screening and monitoring among patients treated with psychotropic drugs, several strategies have been introduced in practice aiming to minimize cardiovascular and metabolic side effects that can be caused by psychotropic medications. These strategies range from simple act such as adding drugs that can reverse or attenuate the adverse metabolic effects of psychotropic drugs to include more complicated behaviour for example adopting a healthy life style (9,31,39). Generally ,strategies can be divided into: pharmacological and non-pharmacological (40).

In the context of mental health conditions, non-pharmacological interventions focus mainly on behavioural changes, in which affected people adopt certain measures for example life style modifications and educational programs. These interventions have been intended mainly to improve physical health in patients with mental health conditions. However, methodological variabilities such as sample size, duration of interventions and differences in intervention approaches themselves make it difficult to make conclusive estimation of their effectiveness. Pharmacological interventions, on the other hand, are strategies refer to acts that concern the use of medications. It may include proper selection of medication, switching between drugs and the use of adjunctive agent. Other forms of pharmacologic interventions such as screening and monitoring of cardiovascular side effects have been addressed in several trials (41–43).

The selection of medication with preferable safety profile can be applied in patients with increased risks for a particular side effect. It includes the proper selection of drug dose and dosage formulation. Switching to a safer drug can be considered when adverse drug effect is suspected (44) or adjunctive drug can be added to attenuate or reverse the side effect of a concomitant agent. Few studies have considered switching for medication with favourable side effects profile as a major intervention to minimize the cardiovascular side effects of the utilized antidepressant drugs (45). Results of a review that investigated the different interventions to manage weight gain and metabolic disturbance in patients taking antipsychotic drugs (31) suggest that pharmacologic interventions primarily, switching between medications along with choosing the proper drug, are considered the most effective strategies to minimise weight gain. This is particularly useful when early non-pharmacological intervention is inadequately effective. However, even when physical

health issues are developed, evidence indicates that may health care professionals tend to be hesitance to switch to psychotropic with better side effects profile. This indicate an urgent need to identify factors that hinder the application of pharmacological interventions in patients treated with psychotropic drugs.

So far, the majority of the proposed strategies to manage cardiovascular and metabolic side effects of psychotropic drugs focus on utilising non-pharmacological approaches. Such strategies are mainly based on behavioural modifications that encourage subjects to adopt behavioural changes which have positive impact on their life. An example of this, programs that are designed to aid weight management and smoking cessation (46). Furthermore, the majority of the proposed work focus on managing weight gain and physical health of patients treated with antipsychotic agents. Number of trials have focused on pharmacological interventions primarily the ones that lessen or antagonise that weight inducing effect of antipsychotic drugs (anti-obesity agents). Among the most commonly investigated agents are metformin and nevertheless, the safety and the clinical efficacy of some of the proposed anti-obesity drugs have not been established yet. Nevertheless, other forms of pharmacologic interventions such as switching between medications are not extensively investigated in the literature. Therefore, it is difficult to rely on this results if we considered that other potential effective approaches such as adding adjunctive drug and switching to safer drug may not be properly undertaken in real practice.

1.4 WHY IT IS IMPORTANCE TO CONDUCT THIS REVIEW?

There is no clear data from systematic reviews and meta-analysis regarding the prevalence of cardiovascular and metabolic comorbidities and their predisposing factors among patients with mental diseases which are associated with the use antipsychotic and antidepressants drugs. As indicated by several epidemiological studies (45) the prevalence of schizophrenia and depression continues to increase, which indicates a potential rise in the prescribing patterns of psychotropic medications worldwide. Furthermore, despite existing guidelines and recommendations, many antipsychotic and antidepressant drug-treated patients are not adequately assessed for easily measurable metabolic and cardiovascular risk factors, such as dyslipidemias and blood pressure (38). Most evidence points out that metabolic and cardiovascular comorbidities in people using antipsychotic and antidepressant medications are underdiagnosed. For instance, data generated form CATIE trial (41), which aimed to examine a multitude of variables in patients with schizophrenia that increases the incidents of metabolic syndrome (MS), demonstrate a significant variation in the level of management among elements of metabolic syndrome (MS). This included lower rate of screening and treatment of major cardiovascular risk factors such as hypertension and dyslipidemias, however, the study did not highlight any possible reasons for this low rate of treatment among the targeted population. Barriers to effective interventions in practice include resisting behaviour of patients with mental health conditions, time constrain and the availability of the necessary equipment may have possible impact.

1.4.1 Rational of the review: (purpose statement)

As proposed above, in order to alleviate cardiovascular and metabolic complications, which can be caused or aggravated by antipsychotics and antidepressants medications, careful follow-up with routine monitoring of cardiovascular disease and its related risk factors side effects at early stages might facilitate successful management of the complications and hence provide better prognosis. In

order to accomplish that, representative epidemiological data are critical in order to estimate the impact cardiac and metabolic related side effect of, mainly antipsychotics and antidepressants, on public health. Beside it is important to review the nature and effectiveness of interventions aimed to monitor and manage the cardiovascular and metabolic side effects of these medicines.

1.4.2 Objectives of the study:

- To identify the prevalence and incidence of cardiovascular and metabolic side effects in patients taking antidepressants and antipsychotic medications.
- To identify the nature of interventions and their effectiveness around assessment, screening, monitoring, management cardiac and metabolic side effects of antipsychotics medications.
- To identify the extent to which patients taking antidepressants & antipsychotics are assessed, screened, monitored and managed for cardiac and metabolic side effects.
- To explore the perspectives of health care providers regarding the assessment, screening, monitoring and management of cardiac and metabolic side effects in patients taking antipsychotic or antidepressant medications.
- To explore patients' perspectives regarding the assessment, screening, monitoring and management of cardiac and metabolic side effects related to the use of antipsychotic and antidepressant medications.

1.4.3 Review questions:

- What are the incidence and prevalence of cardiac and metabolic complications that are correlated to the use of antipsychotic and antidepressant medications?
- What are the different interventions to manage cardiovascular and metabolic side effects of antipsychotic and antidepressant medications that have been proposed in the literature?
- Is there current evidence which support the effectiveness of regular assessment, screening and monitoring of cardiac and metabolic side effects of antipsychotic and antidepressant medications?
- How often patients using antidepressant or antipsychotics are assessed, screened, monitored and for cardiac and metabolic risk?
- What are the possible barriers for assessing, screening and monitoring the targeted side effects in patients using antipsychotics and antidepressants?

2 METHODS:

2.1 REPORTING GUIDELINES:

The review protocol has been drafted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMAP) statement (47). The review will be conducted as per the Cochrane guideline for systematic reviews (48) and Centre for Review and Dissemination (CRD) (49). Reporting of the review including results of the literature searching, screening, data extraction and the applied inclusion and exclusion criteria will conform to Preferred Reporting Items for Systematic Reviews and Met-Analysis (PRISMA) statement and checklist. This review will be part of a dissertation for a doctoral degree. Eligibility criteria for inclusion:

2.1.1 P: Populations

- **P 1**: Adult patients aged ≥ 18 years old.

- Using one or more antipsychotics drugs or antidepressant therapy or a combination, for mental health conditions.
- **P2**: Health care professionals involved in the care of the patients.
- **P2**: Patients prescribed antipsychotics/antidepressants for mental health conditions

Special inclusion criteria for studies to be selected for the prevalence purpose:

- **P3**: patients of all ages receiving antipsychotics or antidepressants or both.

2.1.2 I1: Interventions

Interventions related to the assessment, screening, monitoring of cardiac and metabolic side effects related to antipsychotic and antidepressants.

2.1.3 I2: Phenomena of Interest

Views, experiences, behaviors of health care professionals and patients regarding the assessment, screening and monitoring of cardiac and metabolic side effects of the antipsychotics and antidepressants.

2.1.4 O: Outcomes measures

2.1.4.1 Primary outcomes:

- Incidence or prevalence of cardiac or metabolic side effects of antipsychotics and antidepressants.
- Nature of interventions that are proposed in the literature for example: pharmacological and non-pharmacological interventions.
- Improvement or worsening of pre-existing cardiac or metabolic condition induced by antipsychotics and antidepressants.
- Experience of patients receiving the interventions, for example: Patients' satisfaction with care provided to manage cardiovascular and metabolic complications of antipsychotics and antidepressants.
- Perspectives of health care providers regarding the delivery of care for example, barriers and facilitators to screening or management of cardiovascular side effects and their associated risk factors in patients using antipsychotics and antidepressants.

2.1.4.2. Secondary outcomes:

- Any other patient-reported outcomes other than symptom improvement for example their quality of life.
- Hospitalisation or re-admission primarily related to cardiac or metabolic complications in patients prescribed antipsychotics and antidepressants.
- Health care professionals and patients' awareness, views and experiences of the cardiovascular and metabolic risks associated with the use of antipsychotics and antidepressants.

2.1.5 C1: Context

- Patients with mental health conditions using antipsychotics or antidepressants as major treatment for the primary condition (depression or psychosis).
- Any clinical settings.

2.1.6 C2: Condition

- Prevalence or incidence of cardiovascular and metabolic side effects and their risk factors in patients diagnosed with mental health conditions using mention the two classes of drugs.

2.1.7 S: Study design:

All designs that reported either incidence, prevalence or interventions to manage cardiovascular side effects of antipsychotics or antidepressants medications will be included for the review, however, studies will be excluded if they meet one of the following exclusion criteria:

- Case reports.
- Literature reviews.
- Discussion and view point studies.
- Grey literature
- Abstract only publications.

SEARCH LIMITATIONS: English language only, full text publications and studies focused on human, date limit Studies from year 2003 (last 15 years) and onward will be searched (2003). This date limit also coincides with the warring statements that issued by the the Food and Drug Administration (FDA) regarding the increased risks of diabetes induced by second generation antipsychotic drugs (50).

2.2 SEARCH STRATEGY

2.2.1 Information sources:

2.2.2 Electronic sources:

The following databases will be searched in order to identify for relevant literature including:

- EMBASE
- MEDLINE
- PubMed
- Cochrane Central Register of Controlled Trials
- PsycINFO
- CINAHL

2.2.3 Searching additional sources to locate relevant literature:

- Personal contact: researchers will be contacted if necessary to gain information for clarification purposes and access to raw material when needed.
- Cross-referencing of bibliographies: reference list of the identified relevant studies will be scanned including reviews and primary studies.

2.2.4 List of Search terms:

The search strategy combines 4 facets of search terms:

- Antipsychotic and antidepressants medications.
- Cardiovascular and metabolic related side effects.
- Intervention
- Prevalence

A scoping search will be undertaken against each database to inform how the search terms are being be translated in each database and hence identify the corresponding text words in each database (51). After that they will be tested for their sensitivity to locate the key papers that the researcher is aware of, along with relevant articles which are consistent with the inclusion criteria just before applying the search in all the selected search engines. An extended list for the search terms will be provided in supported document (appendix) and they will be adapted as required for each databases. The search will be conducted in three separate stages in order to fulfil each objective of the study by recovering the relevant articles for per objective.

2.3 STUDY SELECTION PROCESS:

A random testing will be conducted to check the eligibility criteria before running the search for standardization purpose (52). This process will be applied on the first 100 identified articles and the eligibility criteria will be revised as necessary. A two stages approach technique will be applied which involves the analysis of the title, abstract in the first stage then full text (51). Besides, the references of the identified articles will be screened for caching any relevant papers. The selected articles will be uploaded into online data collection form Rayyan QCRI. The selected inclusion criteria will be applied to the eligible articles. Titles and abstract will be reviewed and screened independently by two reviewers. Conflict regarding the results will be resolved by discussion or a third review if the agreement cannot be achieved. For missing data or unclear information, contact with primary investigator will be made as necessary. After duplicates removal, full texts of all the eligible studies will be uploaded into referencing manager software (Mendeley^{R}) where they will be assessed further using a piloted check list of the eligibility criteria the PICOCS and the PIC/O. Any conflicts regarding the appropriateness of the selected articles will be sorted by team discussion. The same process will be applied for the full-text screening step.

2.4 ASSESSMENT OF METHODOLOGICAL QUALITY:

Articles selected for retrieval will be assessed for quality before final data extraction process and specific-design study tools will be employed for this purpose. Quality of the studies will be appraised using standardized critical appraisal instruments from the Joanna Briggs Institute Assessment and Review Instrument (JBI) (53), while the risk of bias in each study and across studies will be assessed using the Cochrane EPOC tool (54).

2.5 DATA EXTRACTION:

For each study that meet the inclusion criteria, data will be extracted by two authors, who will be working independently. Data will be extracted using standard form that was created based on study aim and objectives. The following data will be extracted

- **Study characteristics**: authors, date, settings, country of origins and sample size.
- **Patient characteristics**: demographic data (age, gender, body weight, height, diseases status, drug regiment (mono vs combined drug regiment), type of antipsychotic prescribed, co-comorbidities that could affect the outcome.

- **Outcomes of interest:**

➢ **Quantitative outcomes**:

- **Intervention characteristics'**: type of intervention, exposure characteristics including the duration, frequency, intensity and health care professionals involved.

1. Outcomes for intervention effectiveness to reduce cardiovascular and metabolic side effects of the targeted drugs. For example, number of patients screened per visit, patients mean changes form baselines measures or during follow-up period and improvement of quality of life.
2. All causes of mortality and readmissions due to cardiovascular side effects of antipsychotic and antidepressants drugs such as number of deaths or readmissions after applying the interventions.

❖ **Prevalence outcomes**:

1. Outcomes for prevalence or incidence of cardiovascular and metabolic related factors such as (n: %) patients affected.

- **Qualitative** research finding represented as themes metaphors or categories that will be extracted.

2.6 SYNTHESIS OF THE RESULTS:

For the mixed method approach, the model will be applied in this review will rely on the "building and testing" concept (55).

2.6.1 Quantitative data:

Prevalence of cardiovascular and metabolic related complications in patients using antipsychotics and antidepressants and Interventions to reduce cardiovascular and metabolic complications of antipsychotics. We will enter relevant data information into table of the included studies. Meta-analysis will be conducted when suitable, however, it is anticipated to result in methodological heterogeneity due to the wide variety of included studies in this case, narrative synthesis will be adopted.

2.6.2 Qualitative data: Practitioners and patients prospective

Thematic synthesis will be used to synthesis qualitative data into systematic categories [36]. The results of the qualitative synthesis will be utilized to generate recommendations and to provide any explanations for the results obtained from the quantitative data.

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