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REVIEW

The Relationship Between Antipsychotic-Induced Akathisia and Suicidal Behaviour: A Systematic Review

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Objective: We aim to systematically review evidence for a relationship between antipsychotic-induced akathisia and suicidal behaviour, in order to guide further clinical decision making in this area.

Methods: Several electronic databases (Embase, Medline, Cochrane and PsychINFO) were systemically searched for articles published up to February 2021, using search terms related to akathisia, antipsychotics and suicidal behaviour. Two reviewers independently evaluated all the relevant studies using predetermined criteria and assessed the risk of bias for each included study. The systematic review was conducted in line with PRISMA methodology and reporting.

Results: Following de-duplication, screening and application of exclusion criteria, four eligible studies were identified. All of the available studies were in English and included adult patients. Nevertheless, there was significant variability regarding methodology and overall quality was deemed low due to small sample sizes. There was insufficient data to perform statistical analyses of the results. Of the four studies, two found a weak correlation between antipsychotic-related akathisia and suicidal behaviour, a finding that was not supported by the remaining two studies.

Conclusion: The search yielded very few studies for inclusion. On the basis of the existing evidence, akathisia cannot be reliably linked to the presence of suicidal behaviour in patients treated with antipsychotic medication. However, proactive screening for emerging suicidal behaviour in this vulnerable patient group is advisable. Our findings highlight the pressing need for further research in this area.

Keywords: antipsychotic medication, akathisia, restlessness, suicidal behaviour

Introduction

Akathisia (Greek "not to sit") is a movement disorder characterized by a subjective, inner sense of restlessness and difficulty in staying still and is often related to the initiation of or rapid escalation of antipsychotic medication.[1] Akathisia is commonly accompanied by escalated levels of anxiety, agitation and dysphoric affect. The objective component usually entails various semi-purposeful, complex motor activities, such as pacing around, crossing and uncrossing legs, shifting weight from one foot to another, but these may be subtle or absent in some cases.[2]

A reliable assessment and diagnosis of akathisia can be challenging for several reasons. There is no universal consensus on the definition of "case-ness" nor is there an agreement on the relevant significance of its subjective and objective components. In addition, akathisia can manifest in different degrees of severity and have a wide range of

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non-specific motor features. The condition can be easily misdiagnosed - A mild degree of akathisia may be misattributed to psychotic agitation resulting in further escalation of the offending drug. On the other hand, it can co-occur or be caused by other psychiatric and organic conditions (including acute psychosis, comorbid affective disorders, drug withdrawal states, insomnia, delirium), as well as other psychotropic medication, most commonly antidepressants.[3,4]

However, the timely recognition of akathisia is paramount as is it may cause considerable patient distress and may have an impact on treatment outcomes, leading, for example, to non-concordance and subsequent exacerbation of psychosis.[5] Poor adherence to treatment, along with other risk factors, such as previous history of depressive disorder, substance misuse, agitation or motor restlessness, have been associated with an increased risk of suicide in patients with schizophrenia.[6] Furthermore, in one case control study of inpatient suicides,[7] extrapyramidal side effects (including akathisia) were identified as independent risk factors for completed suicide.

Nevertheless, previous attempts to review[4,8] potential links between akathisia and emerging suicidal behaviour were not systematic and were mostly based on a limited number of case reports and small case series. The majority of these reports of suicidal ideation,[9–11] attempted[12–14] and completed suicides,[15,16] were associated with the emergence of acute akathisia induced by first generation high potency antipsychotics (summarised in Table 1). Although, it has been suggested that the magnitude of the problem may be even bigger due to underreported cases.[8]

A definitive causal link between antipsychotic induced akathisia and suicidal behaviour has not been established to date, possibly reflecting the complexity of the clinical phenomena of both akathisia and suicidal behaviour. For the purpose of this review, we focussed solely on antipsychotic-induced akathisia and did not include studies of antidepressant-related akathisia, as the mechanisms mediating this relationship may be different. Furthermore, a systematic review on antidepressant-induced akathisia and suicidal behaviour has been previously conducted,[17] further highlighting the need for a robust literature review in regards to antipsychotic medication.

Aims of the Study

The main objective of this study was to conduct a systematic review of all available literature in order to assess the evidence supporting or discarding a potential relationship between antipsychotic-induced akathisia and suicidal behaviour.

Methods

This systematic review adhered to the PRISMA guidelines.[18]

Inclusion and Exclusion Criteria

Studies were deemed eligible if a) they included adult participants with antipsychotic-induced akathisia, b) the

Table 1 Summary of Case Studies Supporting Possible Association Between Antipsychotic-Induced Akathisia and Suicidal Behaviour

Study	Sample Size	Main Findings
Van Putten et al[11]	3	3 cases of suicidal ideation associated with akathisia caused by fluphenazine depot injection.
Shear et al[15]	2	2 cases of completed suicide associated with akathisia in male patients treated with depot fluphenazine
Drake and Ehrlich[12]	2	Impulsive suicide attempts associated with akathisia in a young man commenced on haloperidol and a young woman started on fluphenazine depot.
Shaw et al[10]	1	Suicidal and homicidal ideation associated with akathisia in a double blind neuroleptic cross over study – a patient was switched from experimental drug with low dopamine affinity to haloperidol.
Schulte[16]	5	2 cases of suicidal attempts and 3 cases of homicide as a result of akathisia, following administration of haloperidol for acute psychotic symptoms.
Azhar and Varma[14]	3	Three cases of emerging suicidal ideation and suicidal attempts attributed to akathisia by patients commenced on haloperidol.
Padder et al[9]	1	1 case of new onset suicidal ideation associated with akathisia in male patient treated with low dose of aripiprazole
Cheng et al[13]	1	Patient developed akathisia and attempted suicide shortly after being started on pipothiazine depot injection.

diagnosis of akathisia was established using validated rating scales, and c) if a temporal or sequential association between akathisia and the emergence or presence of suicidal behaviour (suicidal ideation, suicide attempts or completed suicide) was considered. All clinical clusters requiring treatment with an antipsychotic medication were taken into account and literature related to "first episode psychosis" was also included. Studies reporting on akathisia due to other possible etiopathogenesis were excluded. Studies which were not in English, reviews, conference abstracts, book chapters or treatment protocols were also excluded.

Search Strategy

Our search strategy was generated by consensus amongst four independent researchers who agreed search terms and eligibility criteria. The following databases in the "Healthcare Databases Advanced Search" Platform was used - EMBASE, Medline, Cochrane, and PsychINFO - inclusive of data from inception to February 2021, using the following terms:

Akathisia OR restless*

AND

Suicid* OR self-harm

AND

Neuroleptic* OR antipsychotic* OR major tranquilizer* OR amisulpride OR aripiprazole OR asenapine OR benperidol OR bromperidol OR cariprazine OR chlorpromazine OR chlorprothixene OR clopenthixol OR clozapine OR dixyrazine OR flupenthixol OR fluphenazine OR fluspirilene OR haloperidol OR iloperidone OR levomepromazine OR lurasidone OR melperone OR olanzapine OR paliperidone OR perazine OR perphenazine OR pimozide OR pipamperone OR promazine OR promethazine OR prothipendyl OR quetiapine OR reserpine OR risperidone OR sertindole OR sulpiride OR thioridazine OR trifluoperazine OR trifluperidol OR triflupromazine OR ziprasidone OR zotepine OR zuclopenthixol.

Study Selection

After de-duplication, all titles and abstracts were screened. The assessment of study eligibility and data extraction included a search of the Cochrane Database of Systematic Reviews. A hand search of relevant studies was conducted independently by two reviewers. In the event of any disagreement, adjudication was sought with two additional reviewers. Authors were also directly contacted for additional information if needed. For the purpose of our review, full text studies were only considered if they were in English.

Data Extraction and Synthesis

The data was extracted independently by two reviewers. A PRISMA diagram detailing the study retrieval process is shown in Figure 1. Initially 362 studies fulfilled our search criteria. After de-duplication and screening, only four relevant studies met the predetermined inclusion criteria. All four studies were rated as low quality mainly due to their small sample sizes.

In addition, there was considerable heterogeneity between individual studies including - aims, study designs, interventions, outcome measures; hence, a meta-analysis could not be performed and a narrative approach to synthesizing data from the studies included in this review was used.

Results

Four studies that met the eligibility criteria were included (Table 2). Of these, two reported an association between antipsychotic-induced akathisia and suicidal behaviour, whereas the other two did not find any correlation. A brief narrative highlighting the main hypotheses and the findings of each of the included studies is outlined below:

Atbasoglu et al[19] conducted a study involving 68 patients with schizophrenia or schizophreniform disorder, who were treated with either typical or atypical antipsychotic medication. The authors used the Barnes Akathisia Rating Scale (BARS), Brief Psychiatric Rating Scale (BPRS), and Hamilton Rating Scale for Depression (HAM-D). Akathisia was reported in 22 (32%) patients (when they scored at least 1 in global rating in BARS) and was significantly associated with higher HAM-D ratings for suicidal behaviour, depersonalization, and agitation. However, there were no statistically significant differences in total HAM-D and BPRS scores between the patients with and without akathisia. The further analysis of the dichotomised data (suicidal (n=15) vs non-suicidal) showed that only the depression/anxiety sub-scores in BPRS and subjective components of akathisia (but not objective or global ratings) in BARS were significantly associated with suicidal behaviour. The limitations of the study were a small sample size, the use of a very low threshold for akathisia case definition and the potential contribution of other factors, such as depressive symptoms, anxiety and depersonalisation.

Another study to explore the relationship between akathisia and suicidal behaviour was conducted by Seemuller et al.[20] In this 8-week double-blind randomized control trial, a total of 296 patients with first episode

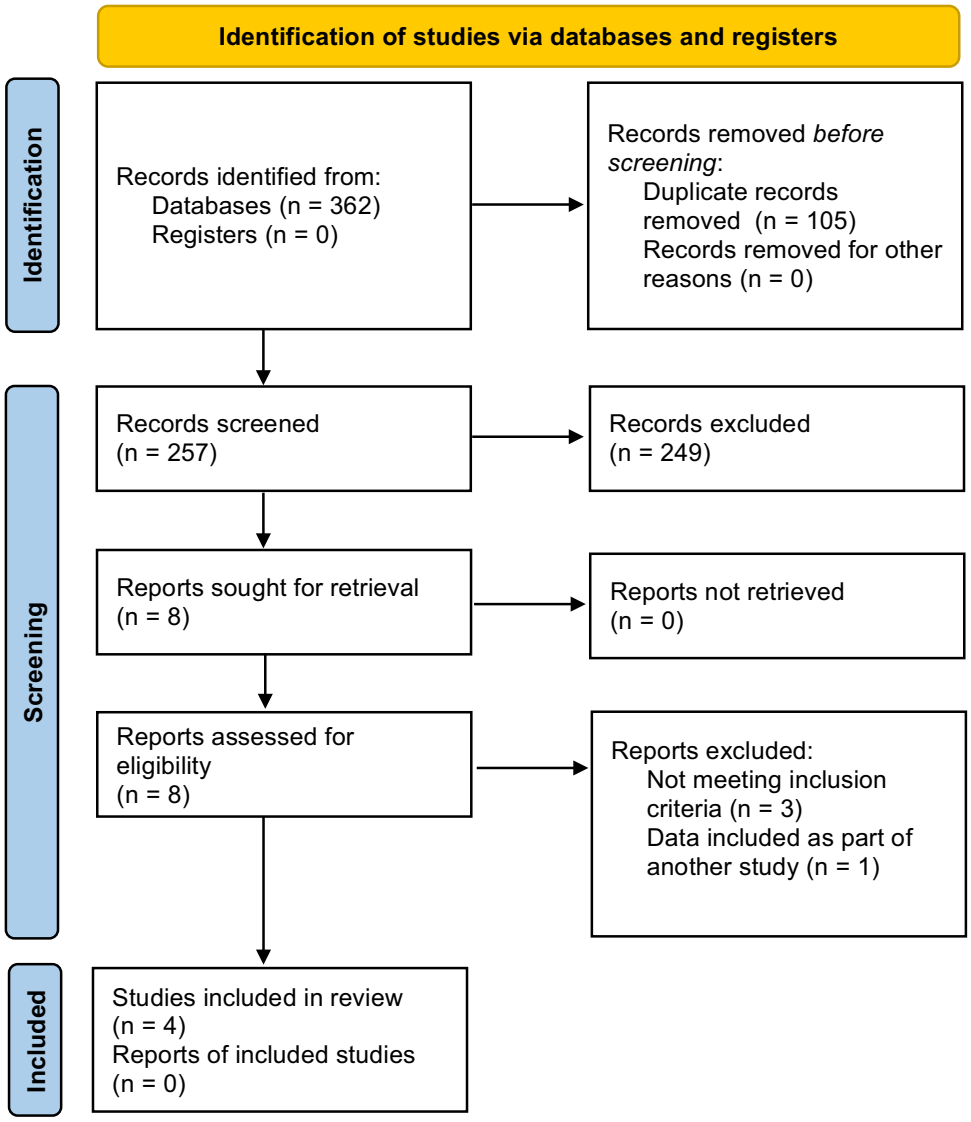

Figure 1 PRISMA diagram. Adapted from Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. Creative Commons license and disclaimer available from: http://creativecommons.org/licenses/by/4.0/legalcode.[18]

psychosis (FEP) were allocated to two treatment arms – either on risperidone (n=148) or on haloperidol (n=148). The mean dose of medication for both groups was 4 mg. In addition, patients were allowed to use rescue medication - biperiden up to 6 mg/d and propranolol up to 80 mg/d - in case of EPS and akathisia. Item 3 of the Hamilton Depression Rating Scale (HAMD) and Hillside Akathisia Scale (HAS) were employed for the assessment of suicidal behaviour and akathisia, respectively. Eighteen percent of patients experienced akathisia with the majority being borderline (10.6%) or mild (6%). The linear regression analysis showed a significant association only between the clinician-rated global akathisia and HAMD score for suicidal behaviour along with depressed mood and use of propranolol; this was not the case for the subjective/self-rated akathisia rating. The log-rank analysis of the time trends between time to maximum akathisia (median – 14 days) and time to maximum score for suicidal behaviour (median – 17 days) did not show any significant differences. Though the authors suggested that there was a correlation between akathisia and suicidal behaviour, they were not able to establish causality between these two clinical phenomena, nor were they able to demonstrate that akathisia precedes suicidal behaviour. They concluded that a much larger sample would be necessary to confirm or reject such hypothesis in the future.

Hansen et al[21] published a sub-analysis of a larger RCT that originally compared the differences between manualized CBT and befriending in patients with treatment

Table 2 Summary of Included Studies

Study	Design	Sample	Main Findings	Quality of Evidence
Cem Atbasoglu et al[19] Turkey	Cross sectional study	68 patients (49 men and 19 women) Mean age: patients with akathisia 33.2 years, without akathisia = 36.7 years	Significant association between subjective components of akathisia, symptoms of depression/ anxiety and suicidality.	Low
Seemuller et al[20] Germany	8 week, double-blind multicenter RCT	289 patients (117 women and 172 men) Mean age: 30.1 years	Significant correlation between objective symptoms of akathisia, depressive symptoms and suicidal ideation in first episode schizophrenia	Low
Hansen et al[21] United Kingdom	Sub-analysis of a RCT	86 at baseline; 67 at second assessment Mean age: 39 years	No significant relationship between akathisia and depression/suicidality in patients with treatment resistant schizophrenia	Low
Hansen et al[22] United Kingdom	Cross sectional study	70 patients (54 men; 16 women) Mean age: 38 years	No correlation found between suicidality and neither akathisia/EPS nor substance abuse	Low

resistant schizophrenia. The authors used the data from two separate assessments – one conducted at baseline (n=86) and the other one after completion of treatment (n=67), which could have lasted up to 9 months. The dose of medication was not altered significantly between the assessments, although there was no information provided on the specific treatments. Patients were assessed using item 7 of the Comprehensive Psychopathological Rating Scale (a non-validated scale for suicidal behaviour), the Montgomery-Asberg Depression Rating Scale and the Barnes Akathisia Scale. 38/86 (44.2%) patients experienced akathisia (scoring at least 1 in BARS) at baseline and 25/42 (59.5%) patients during their second assessment. Neither of the two assessments revealed any statistically significant differences in suicidal behaviour between patients with and without akathisia. Furthermore, there were no significant associations between akathisia and depressive symptoms, or between subjective distress of akathisia and suicidal behaviour.

A different study conducted by Hansen et al[22] included 70 patients (of which 77% were men) with an established diagnosis of schizophrenia, who had been on treatment with antipsychotic medication (first or second generation). Patients also had a history of substance misuse. The BARS was used for akathisia (at least 2 in global score) and a subscale of the Health of the Nation Outcome Scales to assess suicidal behaviour. The rate of suicidal behaviour was not found to correlate with akathisia (or any other EPS), although only the global scores of akathisia were analysed. The study did not account for the use of for additional medication, for example antidepressants or anticholinergics, which could have affected overall outcomes.

Discussion

Despite a vigorous and comprehensive search of available literature, only four studies were identified for inclusion in the systematic review. Results were mostly confined to case reports or case series, often reporting on a very small number of participants. The quality of the included studies was overall low and findings were inconsistent mainly due to methodological issues, potential confounding factors and limited generalisability due to their small non-representative samples.

Of the four studies, two[19,20] reported a weak correlation between antipsychotic-induced akathisia and suicidal behaviour, although discrepancies were noted between the results. Atbasoglu et al[19] suggested that subjective symptoms of akathisia were better predictors of suicidal behaviour than the objective symptoms, while Seemuller et al[20] found that only global ratings of akathisia were associated with increased suicidal behaviour. Nonetheless, both studies were underpowered and unable to establish a temporal association, that is, whether antipsychotic-induced akathisia precipitates suicidal behaviour. In addition, case definition appears to be problematic in the study by

Atbasoglu et al[19] as patients with borderline/questionable pathology were considered as having akathisia.[19]

The other two studies,[21,22] included in this systematic review, could not establish any links between akathisia and suicidal behaviour, although they also had significant methodological flaws. One study[21] originally compared two psychological interventions (CBT vs befriending), which could have potentially ameliorated the effects of akathisia and depression, and the other[22] did not provide any information around concomitant medication (or other psychopathology), which could have also obscured a possible link between antipsychotic-induced akathisia and suicidal behaviour.

Similar to the two negative studies, another study[23] (not included in this systematic review as it was only available as a conference abstract) using validated rating scales and actometry to measure limb movements in akathisia, also failed to find any correlation between the intensity of suicidal ideation and subjective or objective components of akathisia. In contrast, a recent study (also available as conference abstract only) conducted by Bjarke et al[24] reported an association between self-rated akathisia (using a non-validated questionnaire for akathisia) and both depression and suicidal behaviour; a finding that is more in line with the results of the two positive studies[19,20] included in this systematic review.

Previous attempts to investigate potential links between antipsychotic-related akathisia and suicidal behaviour were limited to mainly case reports and small studies. Hansen et al[4] conducted a critical review in 2001 but based on the available evidence was unable to either confirm or unequivocally exclude an association between antipsychotic induced-akathisia and suicidal behaviour. Another review published in the same year by Margolese et al,[8] highlighted the fact that akathisia may be underreported in the existing literature and may, therefore, represent a true risk factor for suicide in schizophrenia.

It is worth noting, that in three out of the four included studies,[19,21,22] patients were receiving long-term antipsychotic treatment. It has been shown that younger and, particularly, antipsychotic naive patients are more susceptible to side effects.[25] This appears to be the case for the majority of the published case reports,[10–16] where mostly young patients were reported to have developed akathisia almost immediately after the initiation of high potency first-generation antipsychotics. Nearly half of the cases of suicidal behaviour were associated with first generation long-acting depot antipsychotics, as described in Table 1. In addition, in a small case series study of 10 patients with first episode of psychosis, Seemuller et al[26] found a close association between rapid-dose escalation and emerging suicidal ideation. In three patients both clinician and self-rated akathisia coincided with emerging suicidal ideation, whereas in two cases only self-rated akathisia revealed a temporal association. Authors highlighted that patient subjective complaints of akathisia should be considered as equally important as the objective signs, as it may help prevent serious harm in this high-risk patient group.

It has been also suggested that acute akathisia may cause a higher degree of inner restlessness compared to chronic akathisia.[27] Sandyk et al[28] attempted to investigate the association between chronic akathisia and previous suicidal attempts in patients with chronic schizophrenia. They found that the severity of akathisia was higher in the group with a history of suicidal behaviour compared to patients with no history. However, due to its retrospective design it was unclear whether patients were experiencing akathisia around the time of their suicidal attempt. Furthermore, other risk factors, such as depression, were not controlled for. Similarly, a fairly recent population-based nested control study by Reutfors et al,[29] looked at the life time EPS history in patients with schizophrenia or schizoaffective disorder who had died of suicide within 5-year period from their initial diagnosis. Eighty-four patients were identified and matched individually with one control from the same study population (N=4000). Interestingly, they found a significantly lower suicide risk for patients with a history of extrapyramidal side effects (aOR 0.33, 95% CI 0.12–0.94); although akathisia was associated with a non-significantly increased suicide risk (aOR 1.21, 95% CI 0.44–3.33) in the absence, however, of any information relating to polypharmacy, adherence to treatment, medication changes or EPS status prior to completed suicide. Due to its retrospective design, authors could not obtain information around the means of assessment of akathisia or a clear chronology of events, which could have suggested a temporal or sequential association with completed suicide. Unfortunately, none of the studies included in this systematic review, differentiated akathisia to chronic and acute subtypes. However, considerations of such distinction might be useful in future longitudinal studies.

Finally, in this systematic review, we have specifically looked into antipsychotic-induced akathisia and not related to antidepressants, where a separate review and meta-analysis had been already performed.[17] Interestingly, it could

not establish any relationship between treatment-emergent adverse effects (including akathisia) and suicidal behaviour in patients treated with antidepressants versus placebo. However, it appears that the analysed clinical trials did not consistently differentiate between suicidal behaviour related to the depressive illness itself and suicidal behaviour associated with medication side effects. A review of 107 articles by Sinclair et al[30] (2009) concluded that an antidepressant-induced jitteriness/anxiety syndrome continues to be poorly characterized and its potential impact on suicide rates has not been sufficiently assessed. In addition, another more recent systematic review and meta-analysis (Sharma et al)[31] highlighted serious limitations in the antidepressant clinical trials and clear evidence of under-reporting of serious harms and adverse events, including akathisia. The authors of the study could not find any significant increase of suicides in association with antidepressants in adult age group, however they highlighted that the true risk of serious harms remains uncertain.

Moreover, given that depression is a well-established risk factor for suicide, it would seem important to explore whether an inter-correlation between akathisia, depressive symptoms and impulsiveness may account for emerging suicidal behaviour rather than akathisia alone in patients with psychosis.[1] On the other hand, establishing the origin of depressive symptoms can be complicated, as they may be directly caused by akathisia, related to the psychotic illness or due to potential dysphoric effects of antipsychotic medication.[32–34]Notwithstanding this, different antipsychotic medication can have variable effects on depression[35] and depressive symptoms are frequently present prior to the commencement of pharmaceutical treatment.[36]

Strengths and Limitations of Our Review

To our knowledge, this is the first systematic review to evaluate the relationship between antipsychotic induced-akathisia and suicidal behaviour. Despite a robust and comprehensive search strategy, the search yielded very few eligible studies. One of the key limitations was their small sample size, which could have contributed to significant outcome variability between the studies. In addition, included studies were of low quality and heterogeneous with regards to methodology, case definition and assessment scales; hence, our review emphasised the lack of relevant literature and a number of limitations in the study design of the existing studies.

It is indeed concerning that this alarming side effect remains potentially under-diagnosed and under-reported. Our findings clearly highlight the paucity of evidence thus far and it is hoped that this systematic review will help emphasize both the importance of patient experience and shared decision making in medication in clinical practice[37] as well the need to prioritise funding and co-produced, participatory research in this area together with service users, carers and clinicians.[38]

Conclusion

On the basis of the limited evidence available, akathisia cannot be reliably linked to the presence of suicidal behavior in patients treated with antipsychotic medication. Furthermore, due to the paucity of high-quality studies, no firm conclusions can be drawn following this systematic review and a possible relationship cannot be discarded either. Nevertheless, the prevention, identification, and timely management of akathisia remain essential, and proactive screening for emerging suicidal behaviour in this vulnerable patient group is advisable. Finally, our findings highlight the pressing need for further research in this area, preferably studies with more robust methodology and adequate sample size.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon request. They are all already in the public domain within the included studies.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

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