Exploring the Overlap of Excessive Daytime Sleepiness, Fatigue and Treatment-Resistant Depression: A Systematic Review

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Abstract

Introduction: Treatment-resistant depression (TRD) is a growing concern with substantial economic implications. In the United States alone, TRD affects 30.9% of adults with major depressive disorder, contributing significantly to the annual economic cost of medication-treated depression.

Objective: This systematic review aims to investigate the connection between excessive day time sleep (EDS) and/or fatigue and TRD. It also explores whether the severity of depression is linked to EDS and/or fatigue in TRD patients.

Methods: Using the PRISMA framework, we conducted an English-language search of four databases spanning 2013 to 2023. Eligibility criteria focused on individuals aged 15 and above diagnosed with TRD, EDS, and/or fatigue assessment in TRD individuals, and its impacts on quality of life.

Results: From 1085 initial records, three studies met the criteria. These studies encompassed 24,316 participants, with diverse findings. One study suggested EDS predicts suicidal thoughts in TRD, while another found no EDS-severity link. The third study indicated increased fatigue in TRD.

Conclusions: While a positive association between EDS, fatigue, and TRD is emerging, caution is warranted due to smaller number and study diversity, varying definition of TRD and co-morbid anxiety. Therefore, future research, particularly randomized control trials, is needed to establish robust conclusions.

Key words: Excessive daytime sleepiness; Fatigue; Treatment resistant depression; Hypersomnolence

Introduction

Treatment-resistant depression (TRD) is commonly defined as the lack of therapeutic response to at least two different antidepressant treatments administered at appropriate dosages for 6 to 8 weeks during a major depressive episode (Fava, 2003; Han et al., 2020). The prevalence of TRD is on the rise, and it is accompanied by a growing economic burden. Approximately one-third of individuals diagnosed with major depressive disorder (MDD) are estimated to experience TRD (Soares et al., 2021). In the United States alone, approximately 8.9 million adults received medication for MDD within a 12-month period, and among them, 2.8 million individuals (30.9%) were identified as having TRD. Furthermore, the overall annual economic cost associated with medication-treated MDD in the U.S. was estimated to be $92.7 billion, with TRD contributing to $43.8 billion (47.2%) of this total (Zhdanava et al., 2021). In another study, the TRD was linked to a 29.3% increase in medical expenses ($P < 0.001$) when compared to patients who did not meet the TRD criteria (Olchanski et al., 2013). Likewise, the individuals suffering from TRD exhibit a higher prevalence of comorbidities, diminished health-related quality of life, an elevated risk of suicide, and increased utilization of both direct and indirect healthcare resources (Soares et al., 2021).

In clinical practice, terms like fatigue and excessive day sleepiness (EDS) are often used interchangeably. Nevertheless, certain studies have identified distinct differences between them (Singh & Husain, 2013). Daytime sleepiness is characterized as excessive when it leads to a subjective complaint or disrupts one's functioning. The International Classification of Sleep Disorders delineates EDS as the incapacity to sustain wakefulness and alertness during the primary waking periods of the day, resulting in unintentional or untimely sleep episodes occurring nearly daily for a minimum of three months (Medicine, 2005). The most commonly utilized scale for measurement of EDS is the Epworth Sleepiness Scale (ESS). The ESS is a concise one-page questionnaire that prompts respondents to self-assess their likelihood of dozing off or falling asleep in various sedentary scenarios encountered in recent times. Respondents rate each item on a scale from zero to three. The individual responses are then tallied to generate a total score, which can range from 0 to 24 (Johns, 1991). In contrast, fatigue encompasses a subjective sense of physical or mental energy depletion. Clinical fatigue comprises three components: an inability to initiate activity, reduced capacity to sustain activity, and difficulties related to concentration, memory, and emotional stability. These distinctions are crucial in understanding and addressing various health issues related to sleep and overall well-being (Markowitz & Rabow, 2007).

In the literature, it is well-documented that daytime sleepiness and fatigue frequently coincide with depression (Corfield et al., 2016; Zhang et al., 2023). Several prior investigations have explored the interplay between depression, fatigue, and EDS, yielding diverse findings (Alonzo et al., 2021; Koutsimani et al., 2019; Sampasa-Kanyinga et al., 2020; Singh & Husain, 2013). In a study by Mume, it was observed that 44.8% of the depressed patients exhibited a mean ESS score of ≥10, indicating the presence of EDS (Mume, 2010). Similarly, in a comprehensive review by Chellapa et al., it was concluded that EDS is a commonly reported complaint among individuals with depression. Despite substantial evidence linking EDS to depression, the precise mechanisms underpinning this association remain unclear (Chellappa et al., 2009). In another systematic review and meta-analysis focused on postpartum depression and fatigue, encompassing thirty-five eligible studies, a robust connection between fatigue and depressive symptoms was established among women during the initial two years following childbirth (Wilson et al., 2019).

Nonetheless, there exists a current void in the literature when it comes to a comprehensive review that integrates the dimensions of TRD, EDS, and fatigue. For this very reason, in recent times, there has been a surging curiosity surrounding the complex interplay among EDS, fatigue, and TRD (M. S. Cepeda et al., 2018; Maruani et al., 2023; Robillard et al., 2019). Hence, the primary goal of this systematic review is to provide clarity by synthesizing the existing research on EDS and fatigue and their significance within the framework of TRD.

Objective

This study aims to explore the relationship between Excessive Daytime Sleepiness (EDS) and/or fatigue with Treatment-Resistant Depression (TRD). Furthermore, it seeks to assess the potential association between the severity of depression and the presence of EDS and/or fatigue in individuals with depressive disorders.

Methods

Search Strategy

In accordance with the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework (Moher et al., 2009), an extensive search was executed across four databases that include PubMed, PsycINFO, ScienceDirect, and Google Scholar, spanning the years 2013 to 2023 and conducted exclusively in the English language. The search terms encompassed a range of relevant keywords such as "excessive daytime sleepiness," "Fatigue," "hypersomnolence," "Hypersomnia," "Idiopathic hypersomnia," "Depressive disorders," "Depression," "Treatment-Resistant Depression," "TRD," "Refractory Depression," "Difficult to Treat Depression," and "Interventions." These keywords were combined using Boolean operators AND/OR to enhance the precision of the search and generate more precise and comprehensive results.

Eligibility Criteria

Preliminary identified reports were reviewed independently by two investigators (N.AL, S.K) and disagreements were resolved by discussion with a third author (S.O) until final consensus was made. Eligibility criteria for this systematic review have been structured according to the PICOS framework as follows:

Population (P): This systematic review's primary focus on individuals above 15 years of age diagnosed with TRD, which is a subgroup of patients with major depression that lack the therapeutic response to at least two different antidepressant treatments administered at appropriate dosages for 6 to 8 weeks (Fava, 2003; Han et al., 2020).

Intervention (I): Assessment and management of EDS in individuals with TRD.

Comparison (C): Depending on the specific objective, a comparison group with a different intervention may be included. However, for the association between EDS and TRD, no comparator group may be required.

Outcome (O): The review intends to evaluate the impact of EDS on the quality of life, considering both overall and individual effects on individuals with TRD.

Study Design (S): The systematic review will include observational studies, randomized controlled trials (RCTs), cohort studies, case-control studies, and cross-sectional studies as eligible study types. It's important to note that opinion pieces, case studies, and non-empirical articles were excluded from consideration. In addition, non-peer-reviewed articles and those lacking full-text availability were excluded. Additionally, we excluded case reports, review articles, editorials, commentaries, letters to the editor, conference abstracts, and animal studies. Moreover, studies primarily centered on conditions unrelated to TRD were excluded, unless they included a subgroup analysis specific to TRD. Furthermore, we excluded studies examining EDS resulting from other medical conditions such as sleep apnea, narcolepsy, or other sleep disorders. Finally, studies focusing on disorders unrelated to our primary objective, such as Multiple Sclerosis (MS) or other neurological conditions, were excluded, unless they specifically addressed EDS in the context of TRD.

Quality Assessment and Data Extraction

The risk of bias in selected studies was assessed using the Newcastle-Ottawa Scale (NOS) (Stang, 2010). This scale comprises distinct criteria tailored to the specific study type, including selection, comparability, and outcome or exposure. It employs a star-based rating system, ranging from zero to nine stars, to evaluate the quality of each study.

During the data extraction phase, a standardized data extraction template was utilized, encompassing various categories of information. These categories included details about the study, its design, the characteristics of the studied population and sample demographics, key outcomes, limitations, and conclusions. To ensure precision and consistency, any discrepancies or inconsistencies that arose during the data extraction process among the authors were resolved through deliberations to achieve a unanimous consensus.

Both reviewers, AB and CD, actively participated in every stage of the literature search, quality assessment, and data extraction process.

Data Synthesis

Due to the significant heterogeneity among the included studies, performing a statistical meta-analysis was not a viable option. Nevertheless, our descriptive analysis offers a thorough and comprehensive view of the outcomes we aimed to explore. We synthesized the results from each study using narrative and thematic methods to provide a well-rounded understanding of the subject matter.

Results

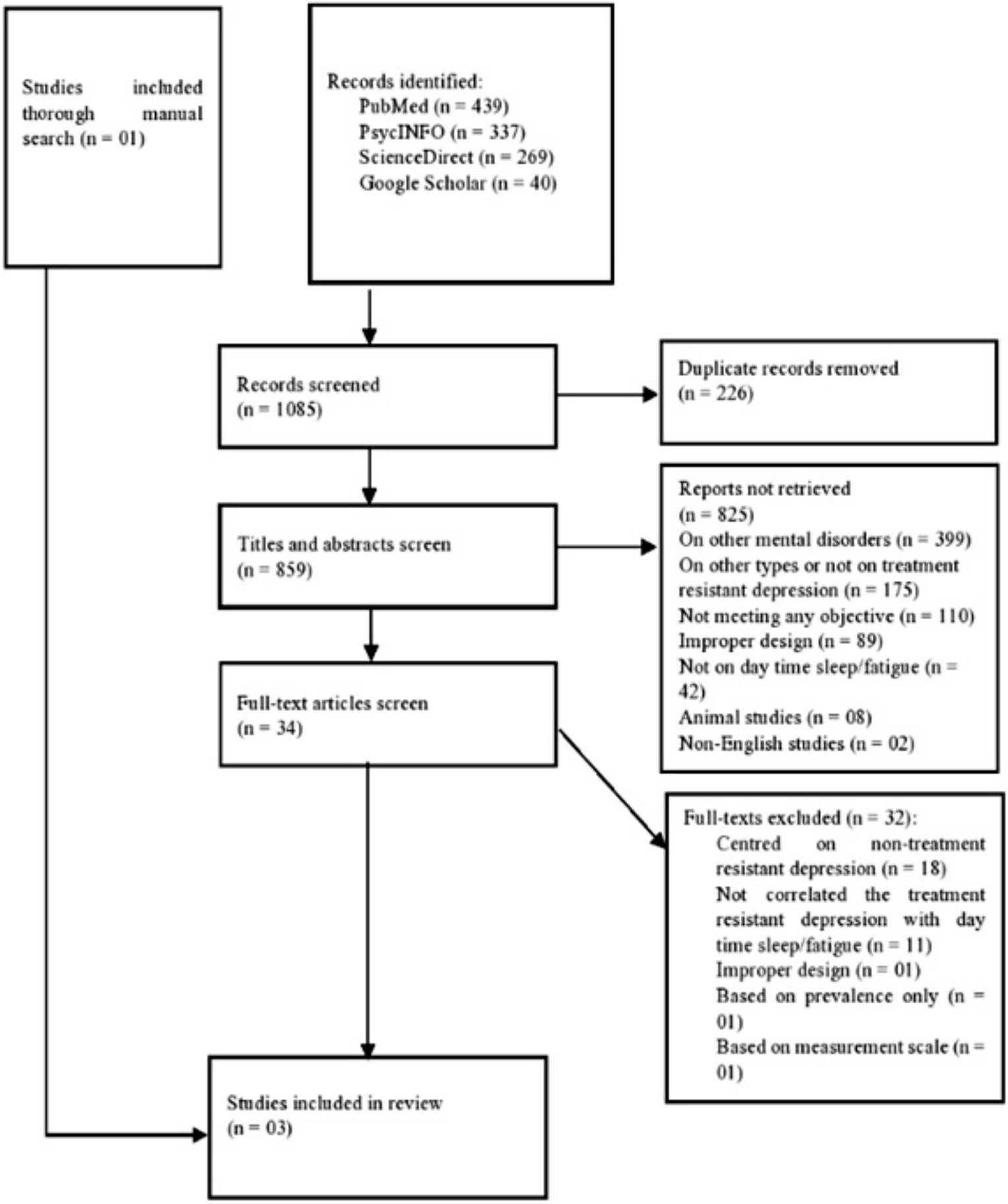
Literature Search

After conducting an exhaustive search across four databases, we initially identified a total of 1085 records. After eliminating 226 duplicate entries, we proceeded to conduct an initial screening based on abstracts and titles for 859 studies. Out of these, 825 studies did not meet the inclusion criteria, as outlined in Figure 01. Following this initial screening, a comprehensive examination of the full texts of the remaining 34 articles led to the exclusion of 32 studies for various reasons, such as not addressing treatment-resistant depression (n = 18), lacking correlation with daytime sleep/fatigue (n = 11), improper study design (n = 01), reliance solely on prevalence data (n = 01), or using an unsuitable measurement scale (n = 01). Ultimately, we selected two studies conducted between January 2013 and June 2023 that specifically investigated the associations between treatment-resistant depression and excessive daytime sleep/fatigue (Figure 1) (M. S. Cepeda et al., 2018; Maruani et al., 2023). Additionally, one study involving adolescents meeting the inclusion criteria (Robillard et al., 2019) was manually identified, resulting in a total of three selected studies.

Quality Assessment and Baseline Characteristics

Within the studies incorporated into the analysis, one of them met seven out of the nine relevant criteria on the NOS (M. S. Cepeda et al., 2018). In contrast, the study conducted by Maruani et al. managed to fulfill six of these criteria (Maruani et al., 2023). Lastly, one study received a rating of only three based on the available data (Robillard et al., 2019). The quality assessment of the included studies is presented in Table 1.

Figure 1: PRISMA flowchart of the searching and screening studies.



Study	Representativeness of exposed cohort*	Selection of non-exposed cohort**	Ascertainment of exposure**	Outcome of exposure*	Comparability**	Assessment of outcome*	Follow up duration*	Adequate follow up*	Total nine**
Maruani et al. 2023	*	*	–	*	*	–	*	*	*****
Robillard et al. 2018	*	*	–	*	–	–	–	–	***
Cepeda et al. 2017	*	*	*	?	*	*	*	*	*****

Table 1: Quality assessment of included studies by using the Newcastle-Ottawa Scale (NOS)

* Comparability was assessed through the following criteria:

A single star was given when the study examined the severity of treatment-resistant depression (TRD), while two stars were assigned if, besides TRD, it analyzed any specific symptoms of TRD.
Complied with the criterion: * Not complied: – Uncertain: ?

In the selected studies, two of the studies followed a retrospective cohort design, while the third adopted a prospective cohort design. These studies involved a total of 24,316 participants with an average age of 35.6 years, comprising 56% women and 39.5% individuals experiencing anxiety. Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS) (Johns, 1991) in two of the studies. In addition to investigating the correlation of day time sleep/fatigue with the severity of TRD, two of the studies also examined its relationship with suicidal ideation and oximetry data. Across the three studies, different definitions were employed to identify TRD. One study used the DSM-IV criteria (Maruani et al., 2023), while another required to have a documented history of undergoing at least two trials of antidepressant medication, each lasting a minimum of four weeks, and exhibit symptoms indicated by a BDI-II score of 14 or higher (Robillard et al., 2019). Further in the third study, TRD was defined to receive three different antidepressants or one antidepressant and one antipsychotic within one year following the index date (M. S. Cepeda et al., 2018). The baseline characteristics of included studies are presented in Table 2.

Table 2: Summary of Characteristics of Included Studies

Study	Design	Sample and demographics	Assessment of daytime sleepiness/ Fatigue	Diagnosis of TRD	Other relevant outcome	Main Findings	Conclusion	Main limitations
Maruani et al. 2023	Prospective cohort study	n = 261; age, 53 (13.3); 60.9% women; 9.7% co-morbid anxiety	Epworth sleepiness scale (ESS)	DSM-IV criteria	Suicidal ideation through suicidal ideation (ISF) scale and the Columbia suicide severity rating scale (CSSRS)	EDS displayed a significant link to suicidal thoughts during the one-year follow-up period (p = 0.035). This association retained its significance even after accounting for confounding variables (p = 0.009). The logistic model further indicated that the presence of EDS at the outset was a predictor of suicidal ideation during the year (OR = 1.7, 95% CI: 1.0–3.3, p = 0.04).	Daytime sleepiness predicts suicidal thoughts in TRD patients	Assessments of sleep patterns relied on self-reported questionnaires and modes sample size raises concerns about its statistical power.

Table 2: Summary of Characteristics of Included Studies (continued)

Robillard et al. 2018	Retrospective cohort study	n = 18; age, 16.8 (0.8); 44% women; 78% comorbid anxiety	Epworth sleepiness scale (ESS)	Documented history of undergoing at least two trials of antidepressant medication, each for a minimum of four weeks, must exhibit symptoms, as indicated BDI-II score of 14 or higher	Oximetry data	39% experienced mild or greater daytime sleepiness. No significant correlations found between either EDS or minimum SaO2% and BDI-II scores (both p > 0.524). EDS was significantly associated with reduced minimum SaO2% (r = -0.51, p = 0.030).	EDS does not predict the severity of depression in TRD	Retrospective data, small sample size, possibility that some patients might have responded to one of anti-depressant, possibility that certain psychotropic drugs interacted with sleep pattern
Cepeda et al. 2018	Retrospective cohort study	n = 24,037; age 36.97; 63% women; 30.7% comorbid anxiety		Receiving three different antidepressants or one antidepressant and one antipsychotic within one year following the index date.		Fatigue exhibited the highest relative risk (RR) at 3.68 (95% CI 3.18–4.25), making it 3.6 times more prevalent in individuals with TRD.	TRD patients tended to be younger and experienced fatigue more frequently.	Retrospective data

EDS, Excessive Day Time Sleep; TRD, Treatment Resistant Depression

Interventional Characteristics of Included Studies
In the three selected studies, one explored the correlation between EDS and TRD (M. S. Cepeda et al., 2018; Maruani et al., 2023), while the third study investigated the association between fatigue and TRD (Robillard et al., 2019).

In the first study conducted by Maruani et al. patients were recruited from a prospective cohort within the French network of TRD expert centers. The study assessed sleep patterns, and circadian rhythms at baseline, and suicidal risk was evaluated both at baseline and during a one-year follow-up using standardized subjective questionnaires. The results indicated that EDS (adjusted odds ratio aOR = 1.7 [1–3.3], p = 0.04) and daytime dysfunction (aOR = 1.81 [1.16–2.81], p = 0.0085) were associated with an increased risk of suicidal thoughts over the one-year follow-up period among patients with TRD, even after adjusting for factors such as age, gender, depression, trauma, anxiety, impulsivity, current daily tobacco smoking, and body mass index (Maruani et al., 2023).

In the second study, which centered on Canadian adolescents diagnosed with TRD, a retrospective chart review was carried out at a tertiary mental health facility. This review involved gathering various data, including results from polysomnography, scores from the Beck Depression Inventory-II (BDI-II), and assessments using the Epworth Sleepiness Scale (ESS). Notably, the study found that 39% of the sample reported experiencing at least mild levels of EDS. However, no significant correlations were identified between EDS and BDI-II scores (both p > 0.524) (Robillard et al., 2019).

Lastly, a retrospective cohort study was conducted utilizing a US claims database. Among the 230,801 patients included in the study, 10.4% developed TRD within the first year. Notably, TRD patients at baseline were younger, with 10.87% falling between the ages of 18 and 19, compared to 7.64% in the non-TRD group (RR = 1.42, 95% CI 1.37–1.48). Furthermore, TRD patients were more likely to have an anxiety disorder at baseline compared to non-TRD patients (RR = 1.38, 95% CI 1.35–1.14). Among the various symptoms assessed, fatigue had the highest RR at 3.68 (95% CI 3.18–4.25) (M. S. Cepeda et al., 2018).

Discussion

Interventional Characteristics of Included Studies
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Conclusions

There has been a growing interest in understanding the intricate relationship between EDS, fatigue, and TRD in recent times. Although a positive association between EDS, fatigue, and TRD has become apparent, it is imperative to approach these findings with caution. This caution arises from several factors, including the observed diversity among the studies, the coexistence of comorbid anxiety, the differing definitions of TRDs, and the utilization of a combination of observational and self-reported data. Consequently, future research endeavors, particularly randomized control trials, are necessary to meticulously evaluate the connection between these variables. Such studies will facilitate the formulation of more robust and reliable conclusions.

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