Pharmacologic Treatment of Antidepressant-Induced Excessive Sweating: A Systematic Review

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ABSTRACT

Background: Antidepressant-induced excessive sweating (ADIES) is a side effect noted to occur in over 20% of patients taking antidepressant medications (Marcy & Britton, 2005). Understanding the effect of pharmacological management of this side effect may allow patients to continue with their current antidepressant medication regimen.
Aims: The aims of this systematic review are to identify medications to successfully manage ADIES, to describe the timeline between initiation of treatment and resolution of ADIES and/or follow-up assessment, and to describe any subgroups that exist related to ADIES treatment efficacy.
Methods: This systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. We conducted a search of ten major electronic databases resulting in 3,922 studies that addressed the pharmacologic management of ADIES.
Results: We identified seven studies that met the inclusion criteria. These studies varied greatly in study methodology and analysis methods used. Although all studies reported positive results from the various interventions used, the degree of bias differed between studies.
Conclusions: The frequency of this side effect and the lack of research on this topic warrant further research into treatment options. The pervasiveness of ADIES also entails enhanced patient education, assessment and management.

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Keywords: antidepressant, hyperhidrosis, diaphoresis, sweating, side effects

INTRODUCTION

Antidepressant prescribing and adherence

Antidepressants are one of the most commonly prescribed classes of medication worldwide, and global use increased significantly between 2000 and 2015, with a 45% increase in some countries[1-3]. In 2015 alone, 150 million prescriptions were written for antidepressants in the United States for the treatment of psychiatric and medical disorders[4]. The goal of antidepressant therapy, regardless of the condition being treated, is to achieve full remission of symptoms with no or minimal side effects[5]. Medication adherence is an important issue in accomplishing this goal and can be one of the largest hurdles to overcome in achieving symptom management[6]. Research has shown that up to 87.6% of individuals who are taking antidepressant medications do not adhere to their prescribed medication regimen[7]. Intolerable side effects, including sexual dysfunction, weight gain, sleep disturbance and excessive sweating, play a large role in non-adherence[6,8].

Antidepressant-induced excessive sweating (ADIES)

Antidepressant-induced excessive sweating (ADIES) is a side effect that has been documented in up to 22% of patients who take antidepressant medications[9,10]. This side effect occurs commonly in all antidepressant classes, including selective serotonin reuptake inhibitors (SSRIs), selective serotonin and norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs)[10,11]. ADIES can be a source of embarrassment for many patients, resulting in impairment in both social and occupational functioning. The loss of fluids caused by ADIES may also pose an increased risk for dehydration or electrolyte deficiency in at-risk populations[10]. ADIES can cause significant frustration for patients who have achieved full or partial remission of their symptoms by taking an antidepressant[12]. Patients who develop ADIES are faced with the decision of either continuing an offending antidepressant medication and living with a side effect that can be difficult to tolerate, or stopping the medication, risking relapse of symptoms, and having no certainty that a new antidepressant will manage their symptoms to the same degree, if at all[11].

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Multiple pathoaetiologies of excessive sweating have been proposed, but the exact underlying mechanisms remain poorly understood. TCAs and SNRIs may result in ADIES by inhibiting norepinephrine reuptake, causing excessive stimulation of peripheral adrenergic receptors, which then produces excessive sweating[10,13-16]. SSRIs and SNRIs have been hypothesised to exert excessive serotonergic effects on the hypothalamus, resulting in disruption of thermoregulation and subsequently causing an inappropriate sweating response[9,11,17,18]. Regardless of the mechanism, ADIES presents a significant risk for low medication adherence and decreases the quality of life for individuals who take antidepressants.

Pharmacological interventions in ADIES

A variety of pharmacological and nonpharmacological approaches are available to address medication-induced excessive sweating. Pharmacological interventions include decreasing the dose of the offending antidepressant, complete change of medication or the addition of a medication that directly targets this side effect.[10,11] Non-pharmacological strategies include behavioural modifications such as reducing anxiety, reducing caffeine and alcohol use, wearing absorbent clothing, and modifying exposure to warm environments[10]. Pharmacological treatment of excessive sweating can be an approach that mitigates this side effect while preventing the discontinuation of an otherwise helpful antidepressant agent.

Study aims

The existing literature related to the treatment of ADIES is sparse compared with that for other antidepressant side effects, and it relies heavily on case reports. To the authors' knowledge, this is the first systematic review to address the topic of pharmacological treatment of ADIES. Thus, the aims of this systematic review were to (a) describe the efficacy of medication used to treat ADIES, (b) describe the timeline between initiation of treatment and resolution of ADIES and/or follow-up assessment, and (c) describe any subgroups that exist related to ADIES treatment efficacy. By understanding the efficacy of medications used to treat ADIES from a systematic review of the literature, health care providers can determine the appropriate pharmacological treatment and treatment trajectory for managing it.

METHODS

This systematic review was conducted and reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[19]

Data sources

The authors conducted a search of ten databases (PubMed, Embase, Web of Science, BIOSIS, CINAHL, JBI Database, PsycINFO, ClinicalTrials.gov, ICTRP Search Portal, and Cochrane CENTRAL), the "times cited" link in Web of Science for included studies, and a reference list of all included studies. This systematic review was registered in PROSPERO, the international prospective register for systematic reviews, to ensure that such a systematic review had not been previously conducted (Registration Number CRD42019089193). The search was performed by using a combination of keywords and truncation when appropriate to capture all relevant variations in terminology. Search terms were categorised into three groups: (a) terms associated with sweat (group 1); (b) terms associated with specific antidepressants (generic and most common brand name), as well as the general term antidepressant (group 2); and (c) the exact phrase "antidepressant induced excessive sweating" (group 3, Table 1). Minor variations in the searches were necessary because of the constraints imposed by interface parameters of the individual databases. The authors can be contacted for specific search strategies pertaining to each individual database. The search was conducted in October 2018.

Inclusion/exclusion criteria

Inclusion and exclusion criteria were determined prior to the screening process to reduce potential bias. Inclusion criteria consisted of studies that (a) referenced ADIES and (b) addressed the pharmacological treatment of sweating related to antidepressant medications. No limitations were placed regarding country or language of origin. No time frame limitations were specified because of the scarce number of studies related to this topic. The earliest study that met inclusion criteria was published in 2002 and the most recent studies were published in 2013.

Exclusion criteria consisted of studies that (a) did not include pharmacological treatment for ADIES, (b) treated sweating caused by essential hyperhidrosis and hyperhidrosis related to a medical condition (i.e. menopause, cancer, etc.), (c) included antidepressants that have been removed from the market, (d) included pharmacological treatment for ADIES that have been removed from the market, and (e) comprised single case reports, unpublished manuscripts (i.e. dissertations), editorials and opinion papers because of the innate low quality of evidence.

Methodological rigor assessment

Methodological rigor was assessed by using tools adapted from the National Heart, Lung, and Blood Institute Study Quality Assessment Tools (which included the Quality Assessment of Controlled Intervention Studies, the Quality Assessment for Before-After (Pre-Post) Studies With No Control Group, and the Quality Assessment for Case Series Studies tools)[20].

Each item for all three tools was scored as 0 (not met), 1 (met), not applicable (equivalent to 0), or cannot determine (equivalent to 0). From the total points, each of the studies evaluated was placed into the category of good, fair or poor quality. The case series tool consisted of nine items with a maximum possible score of 9 points. The quality of case series was determined by the final score after evaluation, with score ranges appraised as good (8-9), fair (6-7) or poor (0-5). The pre-post-test study tool consisted of 12 items with a maximum possible score of 12 points. Pre-post-test quality score ranges were appraised as good (10-12), fair (8-9) or poor (0-7). The randomised control trial (RCT) tool consisted of 14 items with a maximum possible score of 14 points. Final scores for RCTs were appraised as good (12-14), fair (8-11) or poor (0-7). Two reviewers (S.R.T. and L.C.) extracted data from the articles included in this review and independently assessed the quality of included studies depending on the type of study being evaluated. A third reviewer (J.-L.C.), who specialises in systematic review methodology, acted as the tie breaker when consensus could not be reached.

RESULTS

Screening

The original search resulted in 3922 abstracts that were uploaded into Endnote 9.0 for further evaluation. After duplicates were eliminated, a total of 2368 publications were considered for review. Titles and abstracts of the selected publications were then screened for the presence of a pharmacological intervention for treating ADIES, which yielded 44 articles. These 44 full-text articles were screened and those that addressed primary hyperhidrosis, that were single case studies or were letters to the editor were excluded, yielding seven articles that met inclusion criteria (Figure 1). The bibliographies of included studies were hand searched, and promising titles were reviewed to locate articles not catalogued in the major databases. No additional studies were identified in the hand search.

Table 1. Search terminology

Group terms 1 and 2 combined by 'AND' and group term 3 combined by 'OR'				
Combined by "OR" →group term 1		Combined by "OR" →group term 2		Combined by "OR" →group term 3
Group 1 |		Group 2	|	Group 3
Sweating	Antidepressant	Doxepin OR Sinequan	Paroxetine OR Paxil	"Antidepressant
Sweat	Antidepressant drugs	Duloxetine OR Cymbalta	Phenelzine OR Nardil	induced excessive
Hyperhidrosis	Antidepressant*	Escitalopram OR Lexapro	Pipofezine OR Azaphen	sweating"
Diaphoresis	Thymoanaleptics	Fluoxetine OR Prozac	Pirlindole OR Lifril	
	Thymoleptics	Fluvoxamine OR Luvox	Protriptyline OR Vivactil	
	Antidepressive agent	Imipramine OR Tofranil	Reboxetine OR Edronax	
	Antidepressive agents	Isocarboxazid OR Marplan	Sertraline OR Zoloft	
	Amitriptyline OR Elavil	Levomilnacipran OR Fetzima	Setiptiline OR Tecipul	
	Amitriptylinoxide OR Amioxid	Lofepramine OR Gamanil	Selegiline OR Emsam	
	Amoxapine OR Asendin	Maprotiline OR Ludiomil	Toloxatone OR Humoryl	
	Atomoxetine OR Strattera	Melitracen OR Adaptol	Teniloxazine OR Lucelan	
	Bifemelane OR Alnert	Metralindole OR Inkazan	Tranylcypromine OR Parnate	
	Bupropion OR Wellbutrin	Mianserin OR Tolvon	Trimipramine OR Surmontil	
	Citalopram OR Celexa	Milnacipran OR Savella	Trazodone OR Desyrel	
	Clomipramine OR Anafranil	Mirtazapine OR Remeron	Venlafaxine OR Effexor	
	Desipramine OR Norpramin	Moclobemide or Depnil	Vilazodone OR Viibryd	
	Desvenlafaxine OR Pristiq	Nitroxazepine OR Sintamil	Vortioxetine OR Trintellix	
	Dibenzepin OR Noveril	Nortriptyline OR Pamelor	Viloxazine OR Vivalan	
	Dimetacrine OR Istonil	Noxiptiline OR Nogedal		
	Dosulepin OR Prothiaden	Opipramol OR Insidon		

Characteristics of studies included and key findings

Four of the included studies were case series[21-24], two were double-blinded RCTs[12,25], and one study was a non-random quasi-experimental design of a combination of two open-label, uncontrolled clinical trials.[26] The included studies are summarised in Table 2.

Antidepressant medications were used to treat a variety of psychiatric diagnoses in the included studies: agoraphobia (n=1)[21], bipolar II disorder (n=1)[22], depression not otherwise specified (n = 1)[23], dysthymia (n = 3)[24], major depressive disorder (n = 205, including two specified "with psychotic features")[26], panic disorder (n = 2)[25], and obsessive-compulsive disorder (n = 2)[12].

Antidepressant medications implicated as the cause of ADIES included SNRIs (duloxetine [n = 4], 60 mg daily; venlafaxine [n = 9] from 150 mg to 375 mg daily), SSRIs (citalopram [n = 3], 60 mg daily; escitalopram [n = 3] [dosage not reported], fluoxetine [n = 5] from 20 mg to 80 mg daily; paroxetine [n = 2] from 30 to 40 mg daily; sertraline [n = 279] from 25 mg to 100 mg daily), TCAs (clomipramine [n = 3] from 75 to 100 mg daily; nortriptyline [n = 1], 150 mg daily), and aminoketone antidepressants (bupropion [n = 5], 300 mg daily). Dosages were not reported for all patients[12,21-26]. The four case series studies relied on patient reports of sweating severity and side effects as their only outcome measurements and did not report the use of standardised measurement tools[21-24]. The Hyperhidrosis Disease Severity Scale (HDSS) was the most frequently used measurement tool[12,25,26]. Mago et al.[26] used a variety of measurement tools, including the Clinical Global Impression Scale, the Illness Intrusiveness Rating Scale (used in study 2 only), the Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form, and the Systematic Assessment for Treatment-Emergent Events-General Inquiry (study 2 only). Ghaleia et al.[25] also used a self-report side effects questionnaire at the end of the treatment period.

Data extraction and synthesis

Of the four case series studies reviewed, one was rated as moderate quality and three were rated as poor quality[21-24]. The pre-post-test quasi experimental study was rated as poor quality[26]. One RCT was rated as moderate quality and the other as good quality (Tables 3-5)[12,25].

The following data from these seven studies were extracted and synthesised: author; publication year; sample characteristics; offending antidepressant name, class, and dosage; study design; duration; intervention name, dosage, and timing; comparators; blinding methods; outcome measurement tools; analyses; and outcomes, including side effects from the intervention (see Table 2).

The risk of bias was determined with the National Heart, Lung, and Blood Institute Study Quality Assessment Tools. All of the case series studies suffered from selection bias[21-24]. Both of the RCTs reported measures to limit selection bias, including random sequence generation[12] and allocation concealment, but could not exclude selection bias, because only participants who were willing and able to follow the study protocol were included[25]. Both of the RCTs reported measures to limit performance bias (blinding of participants and personnel) and detection bias (blinding of outcome assessors). Ghaleia and colleagues[25] avoided attrition bias

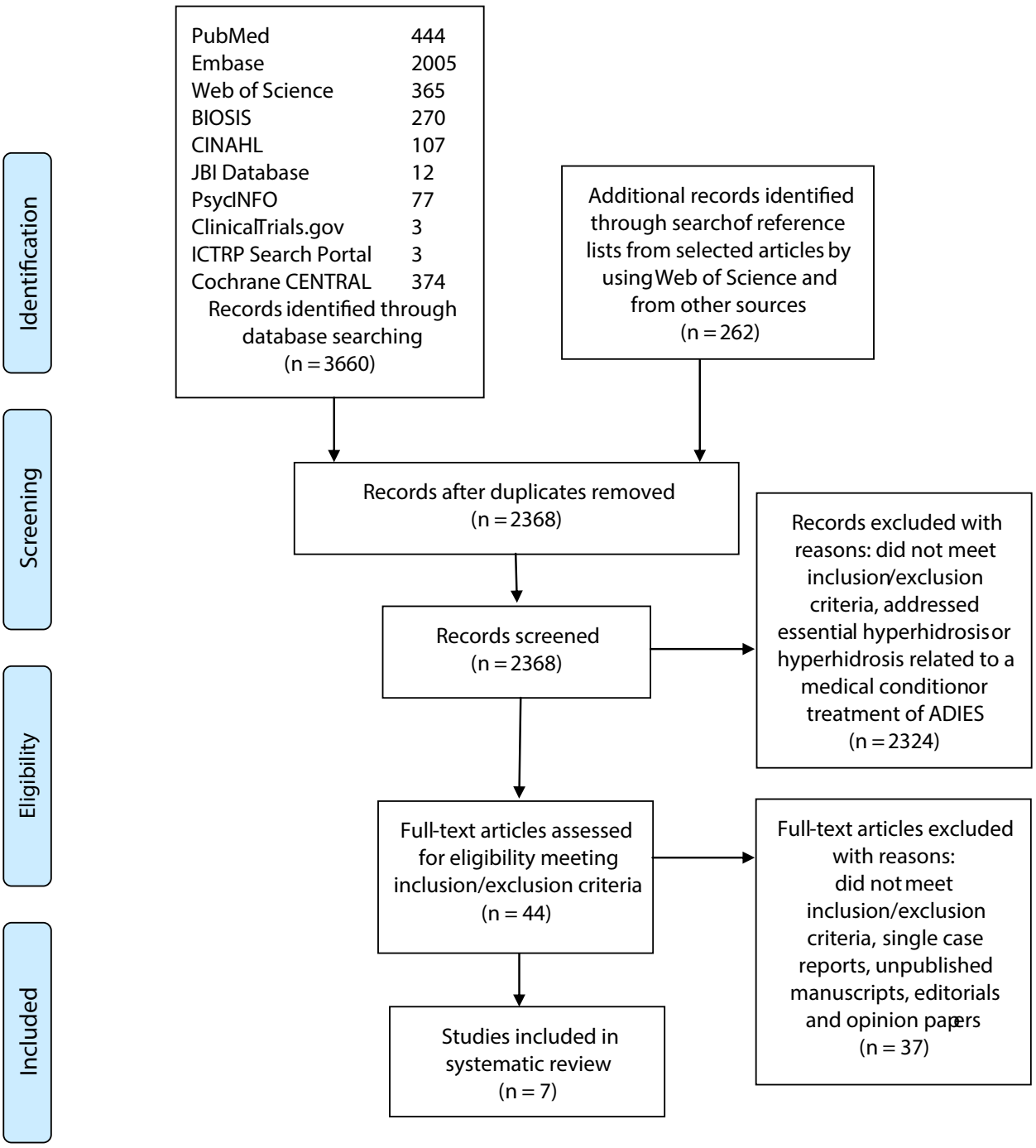

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flow chart. ADIES, antidepressant-induced excessive sweating.

Table 2. Characteristics of included studies

Author(s), date, location	Study type, inclusion criteria, exclusion criteria	Demographics	Offending antidepressant, dosage, class	ADIES treatment medication, dosage, timing	Assessment tool, statistical analysis, blinding	ADIES outcome/ timing of ADIES remission or follow-up
Ashton and Weinstein[21] Location not stated	Case series Inclusion/ exclusion criteria not stated	n = 5 51 y/o male Caucasian, MDD, dysthymia, OCD 65 y/o female Caucasian, dysthymia, OCD 58 y/o male Caucasian, panic disorder, MDD, agoraphobia 56 y/o male Caucasian, MDD 32 y/o female Caucasian, dysthymia	Fluoxetine 40 mg BID (SSRI) Citalopram 60 mg daily (SSRI) Paroxetine 30 mg QHS (SSRI) Venlafaxine 375 mg daily (SNRI) Fluoxetine 40 mg daily (SSRI), venlafaxine 300 mg daily (SNRI)	Cyproheptadine 4 mg BID Cyproheptadine 4 mg QHS Cyproheptadine 4 mg BID Cyproheptadine 4 mg QHS Cyproheptadine 4 mg QHS	No objective measure stated: report of patient No statistical analysis stated No blinding measures stated	No time frame stated/ADIES eliminated and maintained for 1 year Sweating eliminated and maintained for 1 year Sweating eliminated for 9 months Sweating eliminated and ADIEs controlled for 9 months Sweating reduced "markedly" and controlled for over 7 months
Grootens[24] Location not stated Case series	Case series	n = 2 59 y/o male 60 y/o male	Clomipramine 100 mg daily (tricyclic) Clomipramine 75 mg daily (tricyclic), lithium	Oxybutynin 2.5 mg BID Oxybutynin 5 mg TID	No objective measure stated: report of patient No statistical analysis stated No blinding measures stated	Hyperhidrosis resolved in both instances completely. No time frame for re-evaluation of intervention noted in either case
Lu et al.[23] Location not stated	Case series	n = 2 57 y/o female 59 y/o female	Fluoxetine 40 mg daily (SSRI) Duloxetine 60 mg daily (SNRI)	Aripiprazole 10 mg daily Aripiprazole 20 mg daily	No objective measure stated: report of patient No statistical analysis stated No blinding measures stated	Patient 1: completely resolved sweating at 6-month follow-up visit Patient 2: significant decrease in sweating at 2-week follow-up
Mago and Monti[22] Location not stated	Case series	n = 3 57 y/o female 67 y/o male 36 y/o male	Venlafaxine 150 mg daily (SNRI), Wellbutrin 300 mg daily (NDRI) Sertraline 75 mg daily (SSRI) Paroxetine 40 mg daily (SSRI), nortriptyline 150 mg daily (tricyclic)	Terazosin 2 mg QHS Terazosin 2 mg QHS Clonidine 0.1 mg BID	No objective measure stated: report of patient No statistical analysis stated No blinding measures stated	Patient 1: "within a few days, the sweating was 99.99% less" Patient 2: sweating resolved by 75% after 4 weeks, almost complete resolution after 8 weeks Patient 3: 60-70% improved after 3 weeks, follow-up after 2 years indicated ongoing benefit

Ghaleila et al.[25] Behavioral Disorders and Substance Abuse Research Center, Farschian Hospital, Hamadan, Iran	RCT Inclusion criteria: MDD, treated with sertraline for at least 14 days, ADIES related to sertraline, physically healthy Exclusion criteria: HTN, DMII, endocrine disorders, psychiatric morbidity, substance abuse, intolerable side effects from oxybutynin or placebo, pregnancy, breastfeeding	n = 140 Sample size determined to achieve statistical power of 0.80 with type I error of 0.05 Mean age 37.69 ± 10.44 years 86 females (61.4%)	Sertraline: average dosage between 50 and 100 mg daily, mean dosage 83 mg daily SSRI Had to be taking the antidepressant for at least 14 days	Oxybutynin 5 mg daily	HDSS used to assess subjective sweating Comparisons made between control and intervention group conducted by using single t-tests and chi-squared t-tests with respect to demographic data, sweating location, and offending antidepressant dose SPSS version 19.0 for Windows Double blinded	Follow-up assessment occurred after 2 weeks Mean HDSS decreased significantly, P = 0.000; $\eta^2 = 0.668$ Time by group statistically significant for greater improvement in treatment group, P = 0.000, $\eta^2 = 0.139$
Ghaleiha et al.[12] Behavioral Disorders and Substance Abuse Research Center, Farschian Hospital, Hamadan, Iran	RCT Inclusion criteria: MDD, taking sertraline for 4-6 weeks with ADIES Exclusion criteria: medical disorders, substance abuse, any other psychiatric disorder	n = 134 Sample size determined to achieve statistical power of 0.80 with type I error of 0.05, analysis performed with SPSS 16 Age: terazosin 41 ± 13.5 y/o, placebo 38 ± 11 y/o Sex: terazosin male 28 (41%), placebo 29 (44%) Severity of sweating (Grade 4): terazosin 33 (48.5%), placebo 31 (47%)	Sertraline (SSRI) Duration of treatment with sertraline between 4 and 6 weeks Dose range terazosin group 65 ± 30 mg Placebo: 59 25 No significant difference between groups	Terazosin 1 mg at bedtime Initial assessment performed and follow-up occurred at 14 days	HDSS used to assess severity of sweating Fisher's exact test and Mann-Whitney U -test used for comparison of variables without normal distribution, and independent sample t-test used for comparison of numerical variables with normal distribution between terazosin and placebo groups Statistical analysis performed with SPSS 16 Double blinded	Sweating significantly reduced after 14-day follow-up Mann-Whitney U-test showed difference with P < 0.001 Change in sweating outcomes: Grade 4: reduced from 6 to 2 Grade 3: 4 to 0 Grade 2: 28 to 20 Grade 1: 30 to 46
Mago et al.[26] Outpatient services of Thomas Jefferson University, PA	Two open-label, pre-post-test uncontrolled clinical trials Inclusion criteria: age 18-75, diagnosis of MDD, ADIES: moderate severity at least twice a week for 4 weeks, dosage change or changing meds not feasible or helpful for ADIES Exclusion criteria: history of hyperthyroidism, orthostatic hypotension, priapism, abnormal TSH and ED medications	n = 23 Referred by physician and by newspaper advertisements Pre hoc statistics not stated	Venlafaxine (SNRI) n = 5 Duloxetine (SNRI) n = 3 Escitalopram (SSRI) n = 3 Sertraline (SSRI) n = 3 Bupropion (NDRI) n = 2 Citalopram (SSRI) n = 2 Fluoxetine (SSRI) n = 2 Clomipramine (tricyclic) n = 1 Sertraline (SSRI) and bupropion (NDRI) n = 1 Venlafaxine (SRNI) and bupropion (NDRI) n = 1	Terazosin started at 1 mg every night at bedtime, 2 weeks after screening Assessed weekly and increased by 1 mg daily each week to a maximum of 6 mg daily Most common dosage 4 mg daily	HDSS used for screening of sweating severity CGI for excessive sweating was used to evaluate overall improvement IIRS QLES Questionnaire-Short Form Data were analysed with Stata 11.0. No corrections were made for multiple comparisons No blinding measures	All but one patient responded to terazosin; all others noted significant improvement in QOL related to ADIES CGI: median of 5 with range of 4-6 at baseline. Last visit median of 2, range of 1-4 CGI improvement, P < .0001 PGI: scale rate indicated 13 patients considered responsive to treatment HDSS: decreased from median of 3 to median of 1, P = .002 IIRS showed significant improvement, P = 0.003 QLES not significant at 0/483

Table 3. Methodological rigor of included case series

Reference	Study question stated	Study population stated and case definition	Consecutive cases	Comparable subjects	Intervention clearly stated	Outcome measures clearly stated	Adequate length of follow-up	Statistical methods well described	Results well described	MR score
Ashton and Weinstein21	1	1	CD	1	1	0	1	0	0	5/9
Grootens24	1	0	CD	1	1	0	CD	0	0	3/9
Lu et al.23	1	1	CD	1	1	0	1	0	1	6/9
Mago and Monti22	1	1	CD	0	1	0	1	0	1	5/9

1, met requirement; 0, did not meet requirement MR, methodological rigor; CD, cannot determine.

Table 4. Methodological rigor of included pre-post study with no control

Reference	Study question stated	Eligibility criteria stated	Participants representative of population	All eligible participants enrolled	Adequate sample size	Intervention clearly stated	Outcome measures clearly defined	Outcomes assessors blinded	Loss to follow-up 20% or less	Pre and post hoc statistical analysis	ITS design	Group- and individual-level statistical analysis	MR score
Mago et al.26	1	1	1	CD	CD	1	1	0	1	1	NA	NA	7/12

ITS, interrupted time series; 1, met requirement; 0, did not meet requirement; MR, methodological rigor; CD, cannot determine; NA, not applicable

Table 5. Methodological rigor of included RCTs

Reference	Study described as RCT	Adequate Random-isation	Interv ention concealed	Participants and providers blinded	Outcome assessors blinded	Groups similar at baseline	Dropout rate <20%	Dropout rate between groups <15%	Adherence to protocols between groups	Other interv entions avoided	Outcome measures valid and reliable	Adequate sample size shown	Subgroups prespecified	ITT analysis	MR score
Ghaleiha et al.[25]	1	1	1	1	1	1	1	1	1	1	1	1	0	0	12/14
Ghaleiha et al.[12]	1	1	1	1	1	1	CD	CD	1	1	1	1	0	0	10/14

RCT, randomised control trial; ITT, intention-to-treat; 1, met requirement; 0, did not meet requirement; MR, methodological rigor; CD, cannot determine.

by reporting exclusions (n = 5, 3.4%) and reasons for exclusion and did not include them in any analyses. The five attrition cases were excluded because of intolerable adverse effects of the treatment and placebo, yet were not included in their secondary outcomes assessment of side effects, where that data seem relevant[25]. Ghaleia and collegues[12] did not report any attritions or exclusions.

Synthesis of results

What is the effectiveness of pharmacological treatments used to treat ADIES?

Five pharmacological agents were used to treat ADIES in the seven studies that we reviewed.

Terazosin (alpha-1 adrenergic blocker). Terazosin was evaluated in 93 patients in dosages of 1 to 6 mg daily: one RCT (n = 68, fair quality)[12]; one pre-post open-label, uncontrolled clinical trial (n = 23, poor quality)[26]; and one case series (n = 2, low quality)[22]. In all three studies, terazosin greatly reduced the severity of sweating, and the difference between terazosin and placebo reached statistical significance (P < 0.001)[12]. However, there are significant discrepancies in the data (number of patients with Grade IV sweating pre-intervention versus number of patients with Grade I sweating post-intervention) reported by Ghaleia et al.[12] that decreased the validity of their results.

Oxybutynin (urinary anti-spasmodic). Oxybutynin was evaluated in 68 patients in dosages of 5 mg daily in one RCT (n = 66, good quality)[25] and one case series study (n = 2, low quality)[24]. Ghaleia et al.[25] found that the reductions in sweating in the treatment group was statistically significant (P = 0.005), although both treatment and control groups had a notable decrease in sweating at the end of the treatment period (P = 0.03). Grootens[24] also reported that oxybutynin relieved sweating via patient reports.

Cyproheptadine (histamine H1 antagonist/anti-serotonergic agent). Cyproheptadine was evaluated in six patients across two case series studies in dosages from 4 to 8 mg daily (n = 5, low quality[21]; n = 1, low quality[22]). Mago[22] found that cyproheptadine had "minimal benefit" on sweating after several weeks, whereas Ashton and Weinstein[21] reported a reduction in sweating across all patients per patient report.

Aripiprazole (second-generation [atypical] antipsychotic). One case series study (n = 2, low quality[23]) reported improvement in sweating with aripiprazole 10 mg daily, used primarily to treat symptoms of bipolar II disorder and major depressive disorder with psychotic features.

Clonidine (alpha-2 adrenergic agonist). One case series study (n = 1, low quality[22]) reported a 60% to 70% improvement in sweating with clonidine at a dosage of 0.2 mg daily after three weeks in a patient who had not improved with cyproheptadine.

What is the time to resolution of symptoms or outcomes at follow-up assessment?

The timeline between initiation of treatment, improvement or resolution of ADIES, and/or follow-up assessment varied widely between studies, ranging from unspecified to two weeks to multiple years after initiation of treatment medication. The four case series studies did not clearly report duration between initiation of treatment for ADIES and resolution of symptoms, but nine of the 11 patients were followed for at least six months and up to two years.[21-24] Of the case series, only Grootens[24] did not report any time of follow-up or duration of treatment. Mago and colleagues[26] reported two open-label, uncontrolled clinical trials consisting of a two-week baseline period followed by a treatment period of up to six weeks. Both RCTs[12,25] consisted of a two-week treatment period. See Table 2 for details related to timelines for either resolution of symptoms or follow-up assessment of the individual studies.

What subgroups exist related to ADIES treatment efficacy?

In this systematic review, differences in treatment efficacy varied by gender, as reported by one study.

Ghaleia and colleagues[25] found a notable difference in sweating severity by gender, with females experiencing significantly lower mean HDSS scores compared with those of males in both the treatment (oxybutynin) and placebo groups before and after treatment.

DISCUSSION

Summary of evidence/results

Given the prevalence of ADIES and the large number of antidepressant medications prescribed globally each year, there is a surprising lack of data regarding effective treatment strategies. Our systematic review of the literature provides the first critical analysis of the current evidence on the effectiveness of various pharmacological treatments for ADIES in patients who use antidepressant medications. Although the results of this systematic review identified several medications for treating ADIES, the length of effect is undetermined. One study also found that female patients are more likely to respond to medication treatment than are male patients.

Key findings of the effectiveness of the reviewed pharmacological interventions are that a variety of different medications have the potential to reduce or eliminate the severity of ADIES. This effectiveness is likely through a variety of mechanisms of action. It can be hypothesised that terazosin, oxybutynin and clonidine act on peripheral adrenergic receptors to reduce excessive stimulation caused by antidepressants, thereby reducing or eliminating excessive sweating[10,27,28]. Cyproheptadine and aripiprazole can be hypothesized to reduce excessive serotonergic hypothalamic stimulation, which then reduces excessive sweating[10]. Clinicians who are aware of these potential pathoaetiologies of ADIES and the mechanisms of action of these medications can make an educated decision about ADIES management. If a patient has no reduction in sweating with a medication that addresses excessive adrenergic stimulation, then a trial of a medication that addresses excessive serotonergic stimulation would be an appropriate next step. Future research to clarify which medications most effectively address ADIES in the context of antidepressant use would aid clinicians in making a more informed decision regarding ADIES treatment.

A generalized statement regarding the time to resolution of ADIES is difficult because of the variety of offending antidepressants, interventions used and inconsistent documentation of the follow-up evaluation. Within the literature reviewed, the shortest period between initiation of treatment medication and follow-up was two weeks. This suggests that providers may need to wait at least two weeks for any notable decrease in ADIES symptoms. These beneficial effects were also reported to last for years in some patients. Clinicians can use this information to educate patients regarding the expected time frame for ADIES improvement and duration of medication effect. Further research that more accurately assesses the time to reduction or elimination of ADIES would provide a more accurate understanding of these time frames.

Few key findings could be arrived at in the analysis of subgroups in the management of ADIES. The only study that addressed any subgroups was conducted by Ghaleia and colleagues[25], who noted gender differences in the severity of sweating through the evaluation of HDSS scores during both pre- and post-intervention of males and females. Although they did not postulate a hypothesis as to why these differences existed, it may be related to differences in sensitivity to serotonin-modulating medications between genders. Further research to understand the underlying mechanism of action of ADIES is necessary to understand this difference between genders. This would allow clinicians to make informed decisions regarding the potential of medications to evoke ADIES in males versus females.

Although the mechanism of action that results in ADIES is relatively poorly understood, it is clear from the studies reviewed that there are a number of different approaches to managing this side effect. Stakeholders include the patient and the provider who prescribes antidepressants, including, but not limited to, primary care, psychiatry, pain management, neurology and other specialty providers. This variety of possible approaches allows a provider to tailor the management of ADIES to the individual patient, depending on the patient's overall clinical picture and preference. The first step in managing ADIES is to recognise and assess the symptoms, either through self-report of the patient or the use of the validated four-point HDSS[29].

The potential for generalisability of these findings is limited because of the preponderance of low-quality evidence, small sample sizes, and heterogeneity of offending antidepressant medications and interventions used. Implications drawn from this review are that both patients and prescribers need to be aware that excessive sweating is a common potential side effect of antidepressants and that it can be successfully managed with minimal disruption to the patient's antidepressant medication regimen.

Limitations

A number of limitations were encountered in conducting this systematic review, most notably the paucity of high-quality research in the form of blinded RCTs related to this subject. The reliance on case series studies provides weak evidence to support the recommendation of one pharmacological intervention over another. The heterogeneity of study methods used, the variety of offending antidepressant and treating medications, and the lack of high-quality research limited the possibility of conducting a meta-analysis. Notably, none of the studies reviewed addressed patients with excessive sweating caused by antidepressants being used for medical conditions. The risk of bias by the authors of this review is limited because of the rigid nature of inclusion and exclusion criteria, as well as the close collaboration with both a university research librarian and an expert in systematic review methodology.

Recommendations for future research

The literature presented shows that research regarding the management of ADIES is sparse; currently there exist only two published RCTs that focused on two different pharmacological

interventions for treating ADIES, with only one specific offending antidepressant[12,25]. Considering the sheer volume of antidepressants prescribed annually for both psychiatric and non-psychiatric diagnoses, as well as the relative frequency of this side effect, further research on ADIES management is warranted[11]. Additional well-designed RCTs are needed to evaluate the efficacy of all medication interventions noted within this systematic review, as well as other interventions that are efficacious for hyperhidrosis and not discussed herein. Having a variety of well-studied interventions would provide clinicians with the ability to select from robust, evidence-based, patient-centric choices, as well as allowing for multiple options should one intervention be ineffective or intolerable. This research would also expand on our limited knowledge regarding the mechanism of action for ADIES and how to best treat it in the context of different antidepressants and different antidepressant classes.

Conclusion

Hyperhidrosis in any context negatively impacts quality of life and, in relation to antidepressant medications, is particularly debilitating because it compounds pre-existing anxiety, depression and social isolation, which contributes to reduced medication adherence and poor patient outcomes. Considering the increasing rates of use of antidepressant prescriptions for both psychiatric and non-psychiatric diagnosis and the frequency of this side effect, the lack of research on this topic is surprising. This review should serve to prompt future research on ADIES management and encourage prescribers to educate their clients, assess at routine intervals and be deliberate in the management of ADIES.

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