Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 12623 - 12642
Received 05 March 2021; Accepted 01 April 2021.

Drug Related Problems in Type-2-Diabetes Mellitus with and Without Cardiovascular Diseases: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Drug related problems (DRPs) are more prevalent among the type-2-diabetes mellitus (T2DM) patients especially because of related comorbidities and polypharmacy.
Objective: We aimed to quantify the prevalence of different types of DRPs among the T2DM patients with or without cardiovascular diseases (CVD) through a systematic review.
Methods: PubMed/MEDLINE, Scopus and the Cochrane Library were searched to identify the literature till September 2019 from inception. Reference list of all included studies were also searched for additional relevant studies. Studies which assessed the DRPs in T2DM patients with or without CVD published in English language were included in our review. Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields were used to check the risk of bias. Two authors were independently involved in study selection, data extraction and quality assessment of the studies and disagreements were resolved by reconciliation or by consulting a third reviewer.
Results: A total of 34 out of 407 studies considered for the review. The overall prevalence of untreated indications, treatment without indication, inadequate dose, over dose, ineffective treatment, drug interactions and adverse drug reactions was found to be 14.96% (95% Confidence Interval [CI]: 11.86-18.05; 25 studies); 8.54% (95% CI: 6.82-10.27; 23studies); 8.94% 95% CI: 7.11-10.78; 23 studies); 9.20% (95% CI: 3.03-15.37; 23 studies); 17.53% (95% CI: 12.92-22.14; 9 studies); 10.58% (95% CI: 8.66-12.50; 24 studies) and 12.68% (95% CI: 10.52-14.83; 28 studies), respectively. Moreover, DRPs were higher among the T2DM patients with CVD than the patients with T2DM alone. The quality of the included studies appeared to be moderate to high.
Conclusion: Our findings indicate that DRPs were higher among the T2DM patients with CVD than the patients with T2DM alone. There is a need of multi-disciplinary treatment approach to control the prevalence of DRPs.

Prospero registration ID: CRD42020154376

1.Introduction

The latest data from International Diabetes Federation showed that the global prevalence of diabetes mellitus [DM] has reached to 463 million in 2019 and is still undergoing a rapid increase by 2045 to 700 million where in India the prevalence of diabetes was 88 million in 2019 and may increase up to 153 million by 2045[1]. DM is a chronic, progressive systemic metabolic disorder marked by hyperglycaemia. It is associated with abnormalities in carbohydrate, fat, and protein metabolism and results in chronic complications including microvascular [neuropathy, nephropathy, retinopathy] and macrovascular disorders [cardiovascular, cerebrovascular, peripheral vascular diseases] which leads to tissue and organ damage[2]. DM patients are often

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 12623 - 12642
Received 05 March 2021; Accepted 01 April 2021.

accompanied by hypertension and this comorbid condition may lead to serious cardiovascular complications such as heart attack, stroke, and kidney failure[3]. The illness and its complexities experienced by DM patients requires polypharmacy [various medication treatment] which thus can tranquilize drug related problems [DRPs], for example, drug interactions, ADRs, medicine errors, which could lessen levels of prescription adherence[4,5]. A DRP can be defined as any event or circumstances involving the drug treatment, which potentially interferes with the desired health outcomes[3,6]. If DRP's are not solved it may increase Re-hospitalizations, length of hospital stays and expanded financial weight to the patients[6]. However, other factors that may increase the risk of DRPs among the hospitalized DM patients are poor lipid control, cardiovascular disease, renal impairment and the duration of hospital stay[7] . Several studies have been published on DRPs among T2DM with or without cardiovascular diseases [CVD] globally. However, there are no systematic review and meta-analysis done so far, thus our study aims to identify the prevalence rate on types of DRPs in T2DM with or without CVD and tends to provide evidence based approach toreduce the number of DRPs while filling the prescription to the T2DM patients with comorbidities.

2. Materials And Methods

2.1 Protocol registration and reporting

The protocol for this study was already registered in PROSPERO, The International Prospective Register of Systematic Reviews with a registration Number: CRD42020154376 [8]. This review was reported based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses [PRISMA] guidelines for evidence synthesis[9].

2.2 Criteria for inclusion of studies

The analytical studies [interventional and observational] which addressed the DRPs among T2DM patients with or without CVD published in English language studies were considered for our review. Any descriptive studies, reviews, commentaries, editorials, news and conference proceedings were excluded.

2.3 Data sources and search strategy

The literature search was carried out using the following keywords: drug-related problem, DRP, type 2 Diabetes mellitus, type 2 Diabetes with cardiovascular diseases. These keywords were used to search databases, including MEDLINE/PubMed, The Cochrane Library and Scopus for the published studies from inception to September 2019. Any additional published or unpublished studies were searched by checking the references of the included studies. Moreover, Google Scholar, Open Grey and ProQuest were also searched for the grey literature.

2.4 Study selection and data extraction

2.4.1 Study Selection

Title and abstract screening followed by full-text screening of all the retrieved studies was done by two independent reviews [DE and SS] against the pre-defined criteria. Any disagreements in

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the study selection were resolved by the discussion among the reviewers or by the third reviewer [MR].

2.4.2 Data extraction

Data extraction was performed using a pre-framed data extraction sheet by two independent researchers [DE and SS]. The following variables was extracted from the included studies which includes participants' demographic characteristics, study design, setting, and duration, study population, author/year of publication/ country of study origin, methods of analysing T2DM with or without CVD, characteristics of DRP [prevalence, types and most common drug classes], DRP risk factors, and DRP Classification system used. Any disagreements during the data extraction was settled through consensus or the discussion with a third reviewer [MR].

2.5 Risk of Bias and Quality Assessment

Methodological quality of each included study were assessed by 2 independent reviewers [DE and SS] using the Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields [10] , a 14-item measurement tool used to assess the methodological quality of the studies included in a systematic review. Each item/question was scored as 2 [if the response was 'yes'], 1 [if the response was 'partial'], or 0 [if the response was 'no']. Questions that were not applicable to a particular study were marked as 'n/a' and were excluded from the calculation of the summary score, which was calculated for each paper by summing the total score obtained for all items and dividing it by the total possible score. A higher summary score indicated a lower risk of bias and better study quality. Disagreements were resolved by the discussion with a third reviewer [MR/GT].

2.6 Strategy for data synthesis

All the extracted information pertaining to the study and DRP characters and was synthesised qualitatively and presented in a narrative manner. The meta-analysis was performed in Review Manager Software[11] if there is enough quantitative data. The prevalence was extracted as number with percentage and pooled result was presented in the form of percentage along with its 95% confidence interval [CI]. I^2 statistics was used to assess the measure of inconsistency. The random effect model was applied as there was significant heterogeneity [I^2>50%]. A subgroup analysis depends on the presence or absence of CVD with T2DM. No other subgroup analysis was possible because of insufficient data. Publication bias was detected using funnel plot and statistical significance was assessed using the Egger's and Begg's test.

3. Results

3.1 Search and study selection process

A total of 407 studies were identified in the search and 328 non-duplicate studies of them were subjected for initial screening. Among those 247 records were excluded based on the title and abstracts and 81 full-text articles were assessed for the inclusion. Finally, a total of 34 eligible studies were comprising of 17983 participants were considered for the synthesis and analysis. A detailed process of study selection was described in Figure **1**.

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3.2 Data Summary of included studies

The overall duration of included studies ranged from 3 days[12] to 28 months[13] with study participants of T2DM. The cardiovascular comorbidities along with T2DM reported in our studies were hypertension, angina pectoris, Ischemic heart disease, dyslipidaemia, heart failure. All the included studies have varied study designs such as prospective, interventional, randomized controlled trail, retrospective and cross-sectional. The commonly used classifying system was PCNE [Pharmaceutical care network Europe of varied versions] among the included studies. The detailed information on study characteristics is represented in Table **1**.
Table **1: Characteristics of included studies**

3.3 Quality evaluation of included studies

The quality evaluation of 34 studies scores ranged from 80% to 100%, Twenty studies had the maximum score of 100 [4,7,20–28,12–19]. Overall, the quality of the included studies was satisfactory. The quality scores of each study are presented in Table **2.**
Table **2: Quality evaluation of included studies**

3.4 Meta-analysis of Prevalence rate on types of DRPs among included studies

3.4.1 Untreated indication

A total of 25 studies addressed the untreated indication, the overall prevalence of untreated indication appeared to be 14.9% [95% CI: 11.86-18.05; I^2=99%]. There was a substantial heterogeneity among the studies. However, heterogeneity was not reduced by subgroup analysis. Pooled prevalence of untreated indication found to be 12.34% [95% CI: 5.90-18.78 I^2 =99%; 10 studies] among patients with T2DM only and 16.84% [95% CI: 11.69-21.99 I^2=99%, 15 studies] among those with T2DM and CVD which is represented in Figure **2**.

3.4.2 Ineffective provided drug

Pooled analysis of 9 studies estimated that, pooled prevalence of ineffective drug used was 17.53% [95% CI: 12.92-22.14, I^2=99%] with a substantial heterogeneity. The overall prevalence of ineffective drug use was 17.21% [95% CI: 0.04-34.39; I^2 =98%; 3 studies] and 18.90% [95% CI: 12.76-25.04, I^2=99%; 6 studies] among the patients with T2DM only and T2DM with CVD, respectively which is represented in Figure **3**.

3.4.3 Inadequate dose

Meta-analysis of 23 studies demonstrated an overall prevalence of inadequate dose was 8.94% [95% CI: 7.11-10.78; I^2=97%], which was almost similar among the T2DM patients [8.23%; 95% CI: 5.48-10.97, I^2=95%; 10 studies] and T2DM with CVD [9.45%; 95% CI: 6.81-12.10, I2=97%; 13 studies] which is represented in Figure **4.**

3.4.4 Adverse drug reactions

Summary of 28 studies estimated an overall ADR prevalence of 12.68%; [95% CI: 10.52-14.83; I^2=97%], which was comparable in case of patients with T2DM [11.86%; 95% CI: 8.82-14.91,

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I^2=91%; 12 studies] and T2DM with CVD [13.25%; 95% CI: 10.32-16.19, I^2=98%; 16 studies] patientswhich is represented in Figure **5.**

3.4.5 Drug interactions

An estimation of 24 studies addressed the drug interactions, which yielded an overall prevalence of 10.58; [95% CI: 8.66-12.50; I^2=99%], which was lesser among the T2DM [8.91%; 95% CI: 6.67-11.16; I^2=98%; 13 studies] and higher T2DM with CVD [11.87%; 95%CI: 7.82-15.61, I^2=99%; 11 studies], respectively which is represented in Figure **6.**

3.4.6 Overdose

The overall prevalence of high dose was observed to be 9.20 [95% CI: 3.03-15.37; I^2=100%; 23 studies], which was higher than the T2DM patients [5.73%; 95% CI: 3.03-8.44, I^2=97%; 8 studies] and lower than the T2DM with CVD patients [10.93%; 95% CI: 0.94-20.92; I^2=100%; 15 studies] which is represented in Figure **7.**

3.4.7 Unnecessary drug treatment

Pooled analysis of 23 studies demonstrated 8.54% [95% CI]: 6.82-10.27; I^2=98%] of unnecessary drug treatment, which was higher among the patients with T2DM [10.45%; 95% CI: 7.05-13.85, I^2=99%; 9 studies] and lower among the T2DM with CVD [7.77%; 95% CI: 5.24-10.31; I^2=98%; 14 studies] patients, which is represented in Figure **8.**

3.5 Publication bias

An obvious asymmetry was observed with the visual inspection of funnel plot as represented in Figure **9.** However, it was not significant by statistical analysis through Egger's [P=0.793] and Begg's [P=0.186] test.

4. Discussion

The overall mean age of the included studies in this review ranged from 40-75 years. A total of 36 studies with type 2 diabetes with or without cardiovascular diseases comprising of 18,190 participants were included in this study. Among 36 studies, 34 studies with 17,983 participants data was pooled for metanalysis on prevalence rate of different types of drug related problems like untreated indication, ineffective provided drug, inadequate dose, adverse drug reactions, drug interactions, high dose and unnecessary drug treatment. A total of 63,637 DRPs were reported from the included studies. Type 2 diabetic patients were commonly accompanied with hypertension comorbidity which increases the risk of other cardiovascular and cerebrovascular diseases [3] where multiple drugs are to be prescribed for the patients which results in one or the other drug related problems leading to increased hospital stay and economic burden to the patients. Polypharmacy was closely linked with drug related problems which was proved in one of the studies done Malaysia in 2013 emphasizing on significant relationship between polypharmacy and drug interactions [18].
The top most DRPs from included studies were Untreated indication and no optimal therapy reported by Ayele et al[29], Hartuti et al reports that in their study the most common DRPs were

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drug interactions and inadequate dose [30], need for additional drug therapy as reported by Ali et al[26], ineffective provided drug and need of additional drug as reported by Yimama et al[31], drug dose too low as reported by Yschung et al[32], unnecessary use of drugs and improper drug selection are the top most DRPs as reported by Shareef et al [15], drug choice problems and drug interactions were the top most DRPs as reported by Gangwar et al[33], Ahmad et al reports that untreated indication and unnecessary use of drugs were most prominent DRPs[16], potential drug -drug interactions were predominantly reported in the study conducted by Huri et al [17], drug dosing and drug interactions [18], potential drug interactions as reported by Eichenberger et al[34], Adverse drug reactions and wrong dose prescribed were commonly DRPs reported by Granas et al [35], therapy failure and drug choice problems as reported by Roozendaal et al [19], inappropriate use of medicines by the patients was the top most DRPs reported by the study conducted by Haugbolle et al [20], ineffective provided drug and unnecessary use of drugs were the most common DRPs reported by Setter et al[36], drug interactions as reported by Hussein et al [37], untreated indication and drug interactions were top most DRPs reported by Blanc et al [21], unnecessary use of drugs and high dose were DRPs reported in a study done by Benson et al [22], Kovacevic et al reported that ineffective provided drug is the most predominant DRPs in their study[23], additional drug therapy and unnecessary use of drugs were the highest DRPs reported by Westberg et al [24] , untreated indication and drug interactions were the top most DRPs reported in a study conducted by Zazuli et al [3], Steele et al reported that medication under use and unnecessary use of drugs were the commonest DRPs in their study[25], adverse drug reactions and inadequate dose were the most top most DRPs reported by Mendonca et al[13], need for additional drugs and untreated conditions were the commonest DRPs reported by Al-Azzam et al [12], in a study conducted by Ali et al drug interactions were predominant DRPs in their study [26] , untreated indication are top most DRPs reported by Stewart et al [38], the top most DRPs like ineffective provided drug and adverse drug reactions as reported by Kempen et al [27], adverse drug reactions and untreated conditions were the top most DRPs reported by Chua et al [39], Touchette et al reports that adverse drug reactions are the top most DRPs in their study [28], need for additional drug therapy was the commonest DRPs reported in a study conducted by Hall et al[40], high dose and adverse drug reactions were the top most DRPs reported by Scott et al[41], need for additional drug and adverse drug reactions were the most common DRPs reported by Kassam et al[4], Hence, multiple drugs in varied comorbid condition leads to increase risk of DRPs.

The overall pooled analysis on prevalence rate of different types of drug related problems in this study ranged from 8.54% [unnecessary use of drugs] to 17.53% [ineffective provided drug].

5. Conclusions

Polypharmacy results in increased risk of DRPs resulting in inappropriate clinical outcomes therefore regular monitoring and optimizing the drug therapy is needed if patients are with multiple diseases. Our findings indicate that DRPs were higher among the T2DM patients with CVD than the patients with T2DM only. Still, it can be reduced with multi-disciplinary treatment approach

6. Abbreviations

T2DM, type 2 diabetes; CVD, cardiovascular diseases; DRPs, drug related problems; PRISMA,

preferred reporting items for systematic reviews and meta-analyses; EMBASE, excerptamedica database; MEDLINE, medical literature analysis and retrieval system online; CI, confidence interval.

7. Acknowledgements:

Authors would like to thank the staff of department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, MAHE for giving timely suggestions and support for conducting this review.

CONFLICTS OF INTEREST: None of the authors declares conflicts of interest

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Table 1: Characteristics of included studies

S. no	Author, year, Country	Study design	Study Period	Sample size	Mean age	Study participants	Total no. of DRPS	DRP Classification used	Ref
1	Harthuti, 2019, Indonesia	Prospective Observational study	4 months	81	51-60	T2DM	68	Cipolle classification	[30]
2	Ayele, 2018, Harar city	Retrospective cross sectional	4months	203	40-60	T2DM+HTN	364	PCNE V8.02	[29]
3	Yimama, 2018, Ethiopia	Prospective cross - sectional study	2 months	300	54.44 ± 11.68	T2DM+HTN	494	Cipolle classification	[31]
4	Chung ,2017, Hong Kong	ProspectiveObservational study	17 months	522	75.2 ± 5.4	T2DM	417	PCNE V5.01	[32]
5	Al-Azzam, 2016, Jordan	Prospective Cross-sectional study	15 months	2898	56.59±13.5	T2DM	32348	Nil	[14]
6	Shareef, 2015, Mangalore	Prospective Interventional	10 months	151	61-70	T2DM	189	Hepler and strand	[15]
7	Gangwar,2014, Kanpur,	Prospective randomized controlled intervention	12 months	723	20-75	T2DM	723	PCNE	[33]
8	Ahmad, 2014	ProspectiveObservational	24 months	340	60-95	T2DM	992	PCNE	[1

	Netherlands,	study							6]
9	ZamanHuri, 2013,	Retrospective cross-	23 months	208	61±13.3	T2DM+DYS	406	PCNE	[1
	Malaysia	sectional							7]
1	ZamanHuri ,2013,	Retrospective cross-	23 months	200	62.3±12.7	T2DM+HTN	387	PCNE V5.01	[1
0	Malaysia	sectional							8]
1	Eichenberg, 2011,	Prospective cross-	24 months	76	71.4 ± 8.1	T2DM WITH	54	PCNE V5.01	[3
1	Switzerland	sectional, observational				RENAL			4]
						TRANSPAL			
						NT			
1	Granas, 2010, Norway,	Prospective interventional	Not	73	62 years	T2DM	88	PCNE V5.01	[3
2		study	mentioned						5]
1	Roozendaal,2009,	Retrospective Cross -	--	148	61.4±11.8	T2DM	682	PCNE	[1
3	Australia	sectional study							9]
1	Haugbolle, 2006,	Qualitative interview	--	155	51-70	T2DM	635	Nil	[2
4	Denmark	based							0]
1	Setter, 2000, Washington	Descriptive survey design	--	105	62	T2DM	105	Nil	[3
5									6]
1	Husseina,2018,	Retrospective	7 months	278	66.19±	T2DM+HTN	1762	PCNE V5.01	[3
6	Egypt	Observational study			12.90	+DYS			7]
1	Abu Farha, 2019, Jordan	Retrospective cross-	3 months	91	61.1	T2DM	571	PCNE	[4
7		sectional study							2]
1	Blanc, 2018,	Prospective interventional	2 months	297	67±16	T2DM	909	Nil	[2
8	Switzerland	study							1]
1	Benson,2018,	Multi centric Prospective	6 months	493	67.7 years	T2DM+Astha	1124	The Second	[2
9	Western Sydney	observational study				ma		Granada	2]
								Consensus DRP	
								Classification	
2	Kovacevic,2017,	Prospective	4 months	388	72.1±6.3	T2DM+HTN	964	Nil	[2
0	Serbia	observational study				+DYS+			3]
						AP+ CA+			
						Asthma			
2	Al-Taani, 2017, Jordan	Multi-centre, cross-	15 months	1494	58.4	T2DM	1494	Hepler and	[7]
1		sectional						strand	
2	Westberg,2017,	Retrospective	24 months	408	67.7 ±	T2DM+HTN	1033	Nil	[2
2	Minnesota	observational study			13.8	+			4]

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						COPD+CKD +CA			
23	Zazuli,2017, Indonesia	Prospective Cross-sectional	3 months	90	57.73 years	T2DM+HTN	261	PCNE V5.01	[3]
24	Steele, 2016, Kansas City	Pre-/post intervention study	5 months	25	76-92	T2DM+HTN +DYS	85	Nil	[25]
25	Mendonca, 2016, Brazil	Retrospective descriptive study	28 months	92	63.0 years	T2DM+HTN +DYS	316	Cipolle, Strand and Morley	[13]
26	Azzam, 2016, Jordan	Non-randomized controlled trial	3 days	258	54.4±12.1	T2DM+HTN +DYS	258	Nil	[12]
27	Ali, 2015, Pakistan	Prospective observational	3 months	15	54 years	T2DM	33	PCNE V6.2	[26]
28	Stewart, 2015, Putts burg	Prospective observational study	12 months	1842	41.5 years	T2DM+HTN +Asthama+COPD+CVD+ Osteoporosis	673	Nil	[38]
29	Kempen, 2013, Netherlands	Retrospective cohort study	9 months	4,579	75.6 ±10.9	T2DM+CVD +Osteoporosis	13366	Nil	[27]
30	Chua, 2012, Malaysia	Multi centric trail	6 months	477	47.9 years	T2DM+DYS	706	PCNE V5.01	[39]
31	Touchette, 2012, Chicago	Randomized controlled clinical trial	25 months	637	74.5 ± 6.6	T2DM+HTN +DYS+HF	1083	PCNE V5.01	[28]
32	Hall ,2011, Pittsburgh	Random screening	18 months	68	57 years	T2DM+HTN +DYS+HF+Asthama	170	Nil	[40]
33	Scott, 2010, Minnesota	Prospective Cross-sectional, pilot study	11 months	130	86 years	T2DM+HTN +CVD+Hyperlipidemia	304	Cipolle and Strand	[41]
34	Kassam, 2007, Canada	Retrospective cohort study	24 months	138	79.6±4.9	T2DM	276	Nil	[4]

T2DM: type2 diabetes mellitus, HTN: hypertension, DYS: dyslipidaemia, HF: heart failure, CKD: chronic kidney disease, CA: cardiac arrhythmias, COPD: chronic obstructive pulmonary disease

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Table 2: Quality evaluation of included studies

S. No	Question/ objective sufficiently described?	Study design evident and appropriate?	Method of subject/ comparison group, if applicable] selection or source of information/ input variables described and appropriate?	Subject [and comparison group, if applicable] characteristics sufficiently described?	If intervention and randomization was possible, was it described?	If interventional and blinding of investigators was possible, was it reported?	If intervional and blinding of subjects was possible, was it reported?	Outcome and [if applicable] exposure measure[s] well defined and robust to measurement / misclassification bias? Means of assessment reported?	Sample size appropriate?	Analytic methods described/justified and appropriate?	Is some estimate of variance reported for the main results?	Control for confounding?	Results reported in sufficient detail?	Conclusions supported by the results?	Max Qual Points	Total Points	Summary [Percentage]	Ref
1.	2	2	2	2	N/A	N/A	N/A	2	2	2	0	N/A	2	2	20	18	90%	[30]

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2.	2	2	2	2	N/A	N/A	N/A	2	2	2	1	0	2	2	20	18	90%	[29]
3.	2	2	2	2	N/A	N/A	N/A	2	2	2	1	N/A	2	2	20	19	95%	[31]
4.	2	2	2	2	N/A	N/A	N/A	2	2	2	1	N/A	2	2	20	19	95%	[32]
5.	2	2	2	2	N/A	N/A	N/A	2	2	2	2	N/A	2	2	20	20	100%	[14]
6.	2	2	2	2	N/A	N/A	N/A	2	2	2	2	N/A	2	2	20	20	100%	[15]
7.	2	2	2	2	N/A	N/A	N/A	2	2	2	2	N/A	2	1	20	19	95%	[33]
8.	2	2	2	2	N/A	N/A	N/A	2	2	2	2	N/A	2	2	20	20	100%	[16]
9.	2	2	2	2	N/A	N/A	N/A	2	2	2	2	N/A	2	2	20	20	100%	[17]
10.	2	2	2	2	N/A	N/A	N/A	2	2	2	2	N/A	2	2	20	20	100%	[18]
11.	2	0	2	2	N/A	N/A	N/A	2	2	2	2	N/A	2	2	20	19	95%	[34]
12.	2	0	2	2	N/A	N/A	N/A	2	2	2	2	N/A	2	2	20	18	90%	[35]
13.	2	2	2	2	N/A	N/A	N/A	2	2	2	2	N/A	2	2	20	20	100%	[19]
14.	2	0	2	2	N/A	N/A	N/A	2	2	2	2	N/A	2	2	20	20	100%	[20]
15.	1	2	1	2	N/A	N/A	N/A	1	0	1	1	N/A	2	2	20	13	65%	[36]
16.	2	2	2	2	N/A	N/A	N/A	2	2	1	2	N/A	2	2	20	19	95%	[37]
17.	2	2	2	2	N/A	N/A	N/A	2	1	2	2	N/A	2	2	20	19	95%	[42]
18.	2	0	2	2	N/A	N/A	N/A	2	2	2	2	N/A	2	2	20	20	100%	[21]

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19.	2	0	2	2	N/A	N/A	N/A	2	2	2	2	N/A	2	2	20	20	100%	[22]
20.	2	0	2	2	N/A	N/A	N/A	2	2	2	2	N/A	2	2	20	20	100%	[23]
21.	2	0	2	2	N/A	N/A	N/A	2	2	2	2	N/A	2	2	20	20	100%	[7]
22.	2	0	2	2	N/A	N/A	N/A	2	2	2	2	N/A	2	2	20	20	100%	[24]
23.	2	0	2	2	N/A	N/A	N/A	2	2	2	2	N/A	2	2	20	20	100%	[3]
24.	2	0	2	2	N/A	N/A	N/A	2	2	2	2	N/A	2	2	20	20	100%	[25]
25.	2	0	2	2	N/A	N/A	N/A	2	2	2	2	N/A	2	2	20	20	100%	[13]
26.	2	1	1	2	N/A	N/A	N/A	2	1	2	2	N/A	2	2	20	20	100%	[12]
27.	2	0	1	2	N/A	N/A	N/A	2	1	2	2	N/A	2	2	20	18	100%	[26]
28.	2	1	1	1	N/A	N/A	N/A	2	1	2	2	N/A	2	2	20	16	80%	[38]
29.	2	2	2	2	N/A	N/A	N/A	2	2	2	2	N/A	2	2	20	20	100%	[27]
30.	2	2	2	2	N/A	N/A	N/A	1	2	2	2	N/A	2	2	20	19	95%	[39]
31.	2	2	2	2	N/A	N/A	N/A	2	2	2	2	N/A	2	2	20	20	100%	[28]
32.	2	0	2	2	N/A	N/A	N/A	2	1	2	2	N/A	2	2	20	17	85%	[40]
33.	2	1	2	2	N/A	N/A	N/A	2	2	2	2	N/A	2	2	20	19	95%	[41]
34.	2	2	2	2	N/A	N/A	N/A	2	2	2	2	N/A	2	2	20	20	100%	[4]

0, if the response is ‘no’; 1, if the response is ‘partial’; 2, if the response is ‘yes’; N/A, not applicable

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Figure 1. Prisma flowchart of included studies

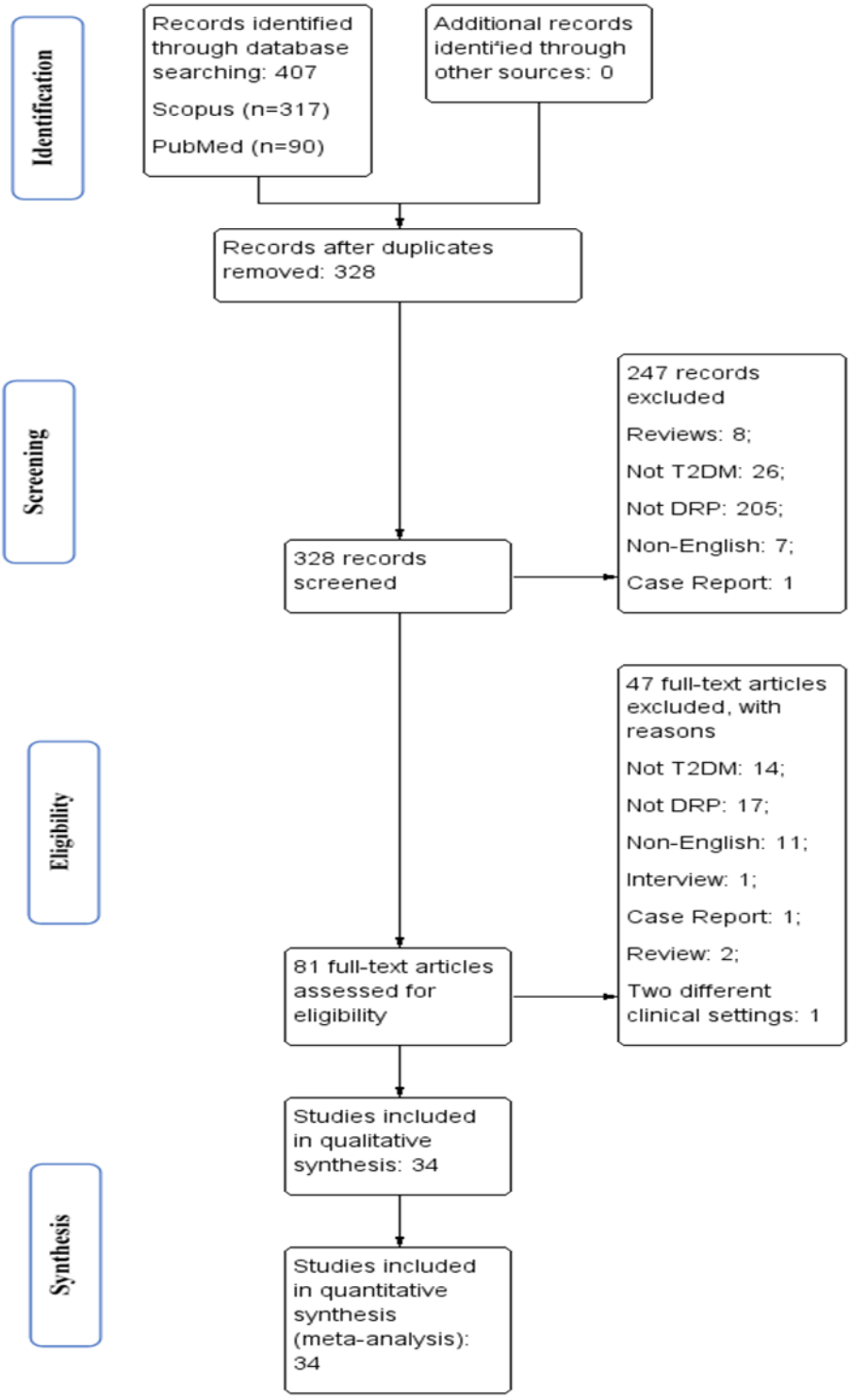

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Figure 2. Metanalysis of Untreated indication

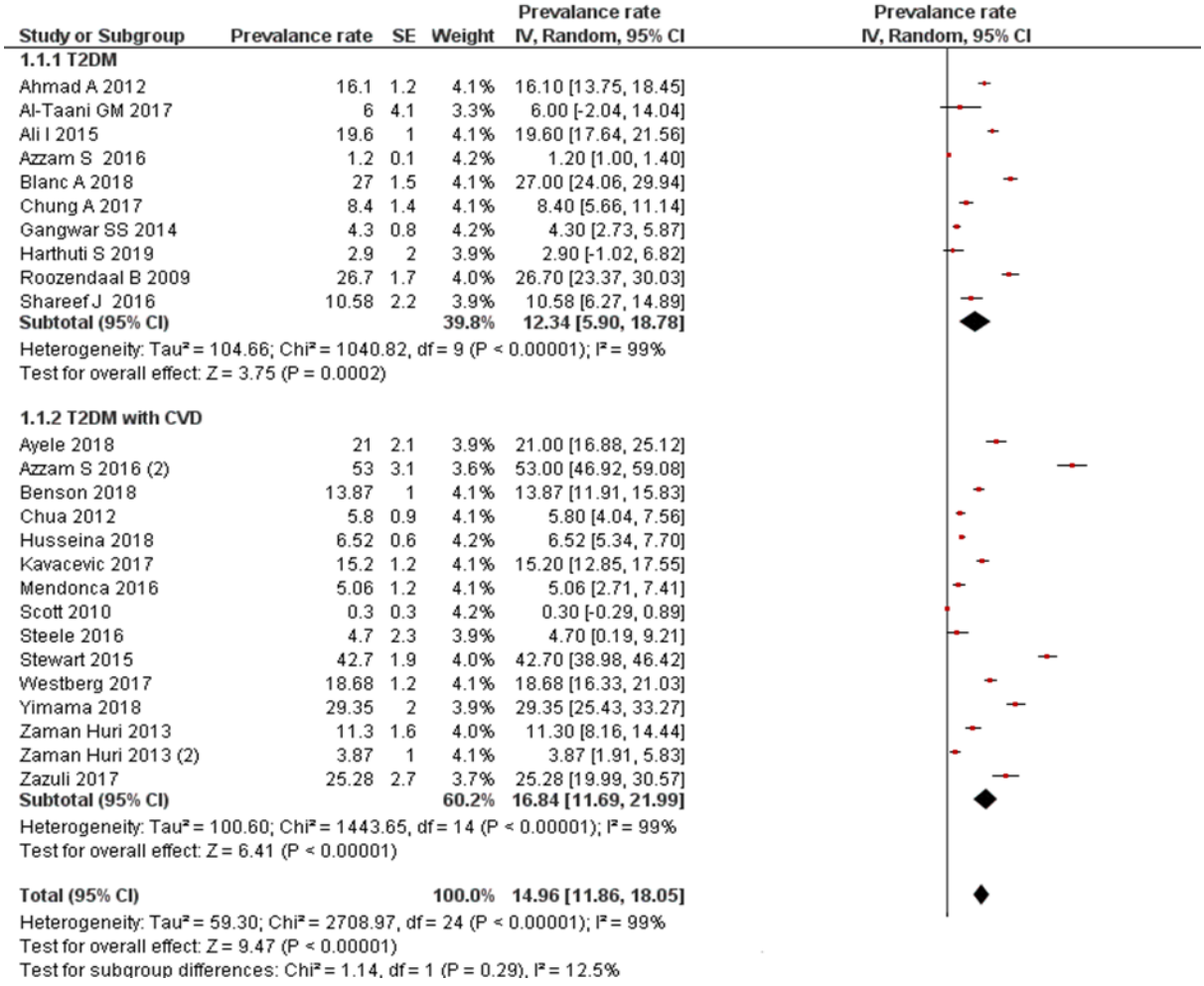

Figure 3. Metanalysis of Ineffective provided drug

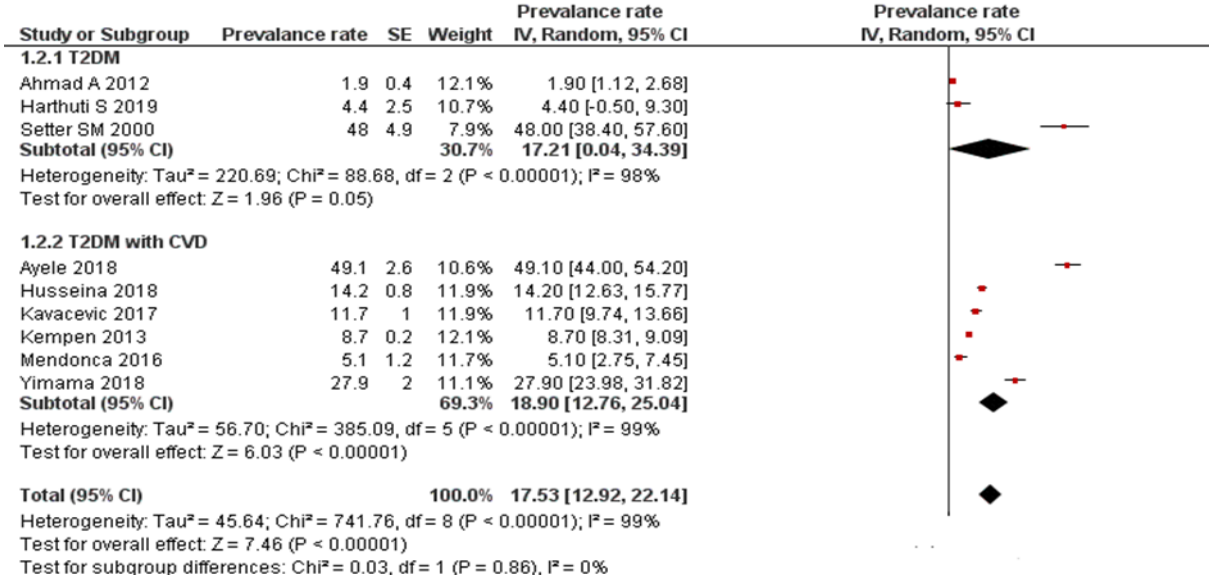

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Figure 4. Metanalysis of Inadequate dose

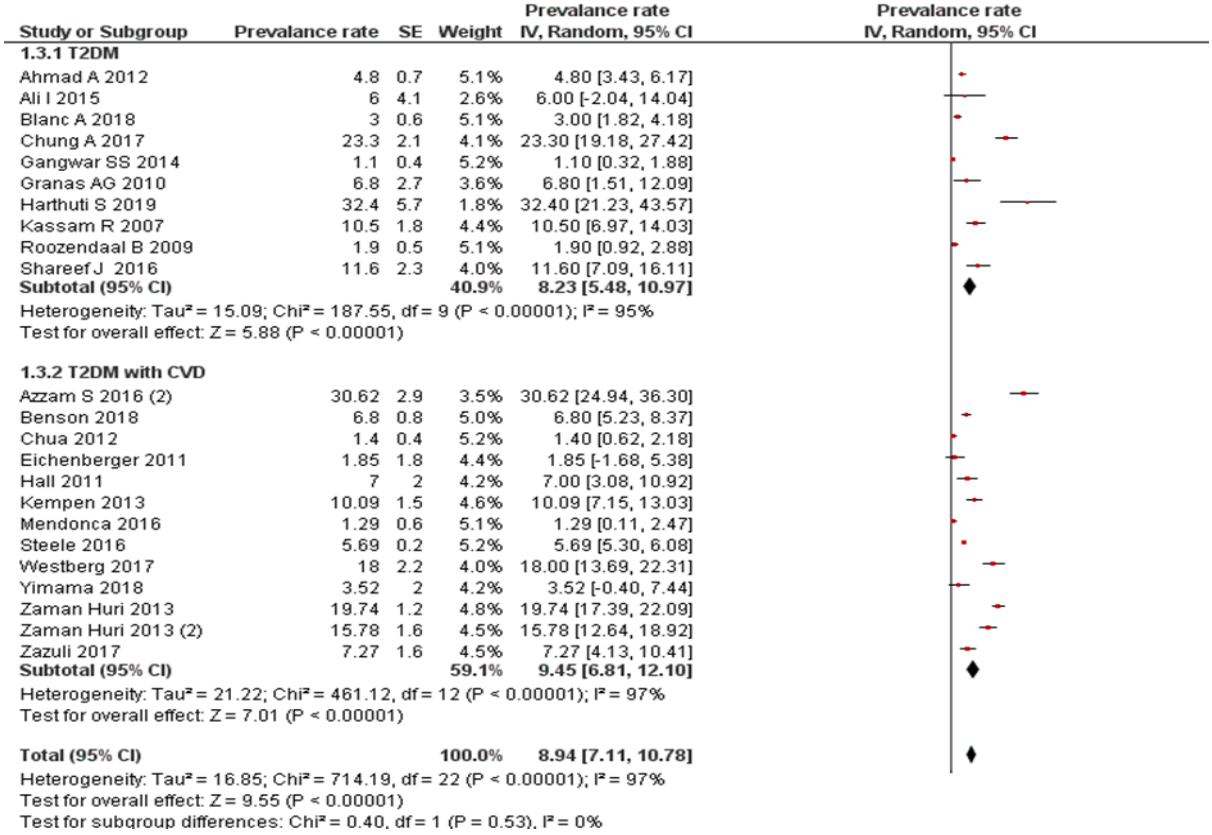

Figure 5. Metanalysis of Adverse drug reactions

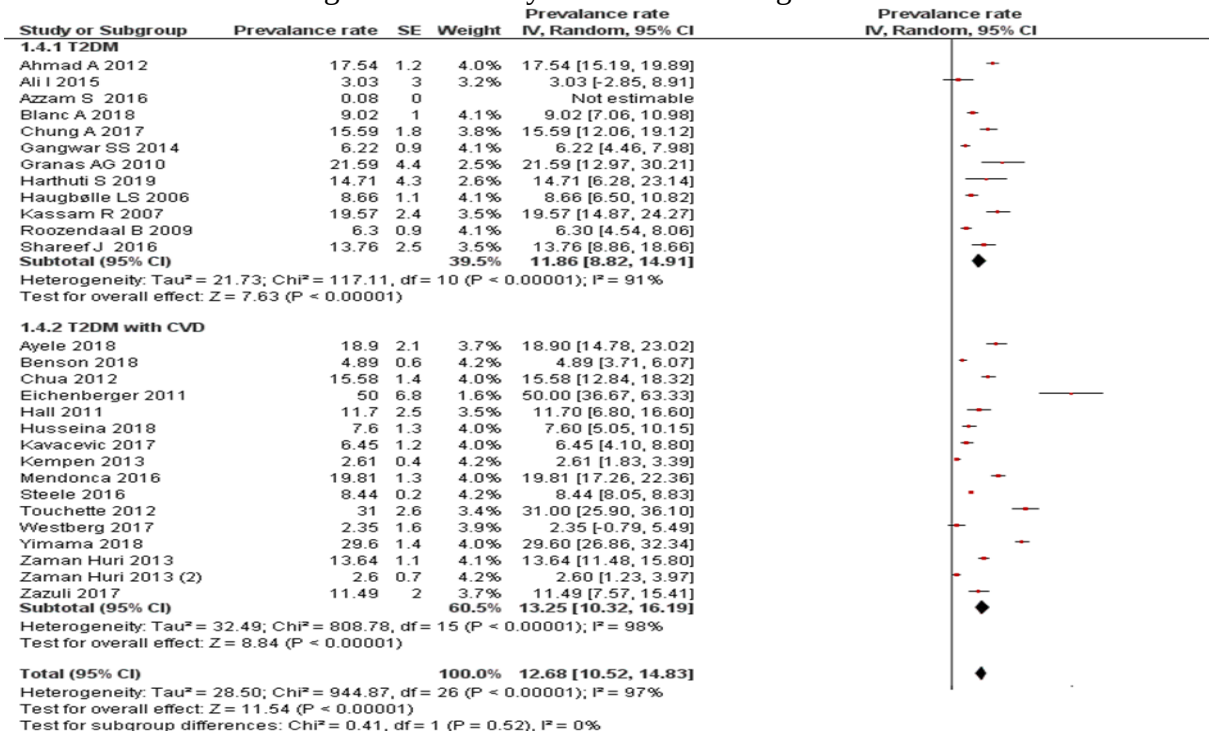

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Figure 6. Metanalysis of Drug interactions

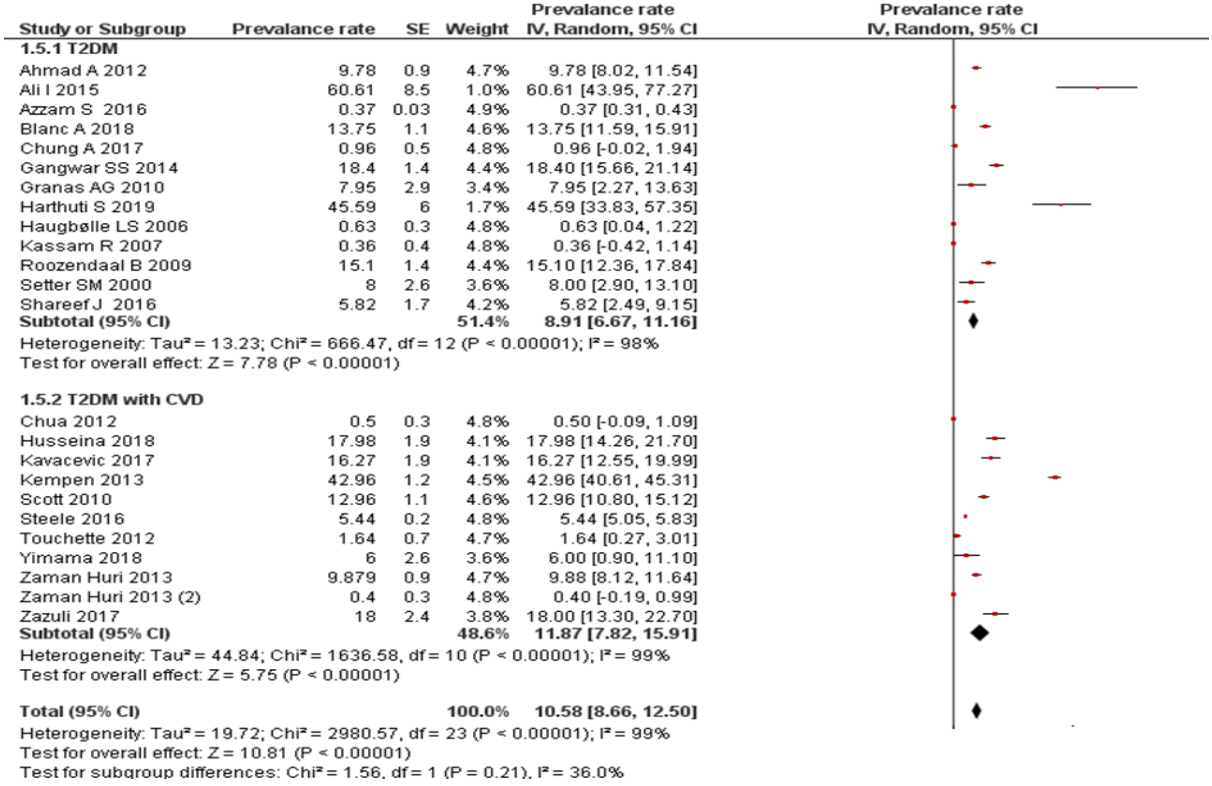

Figure 7. Metanalysis of Overdose

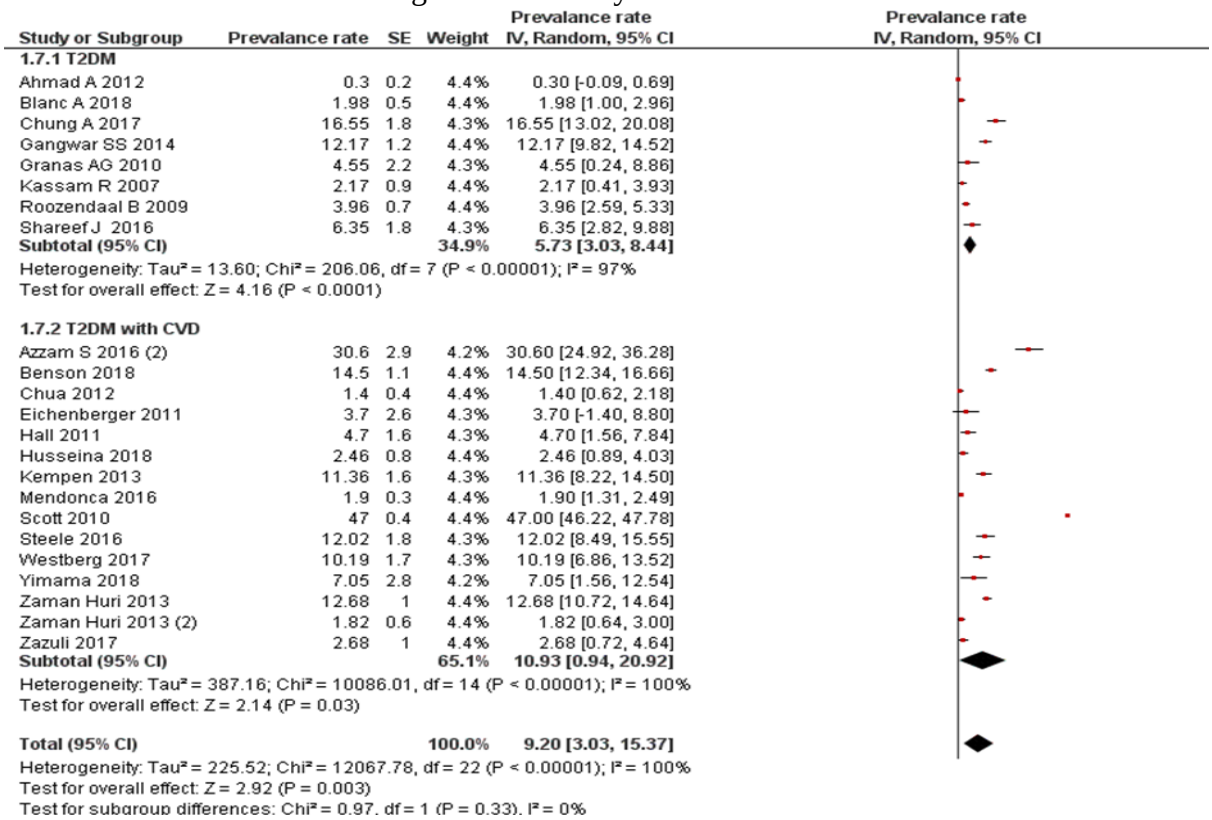

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Figure 8. Metanalysis of Unnecessary drug treatment

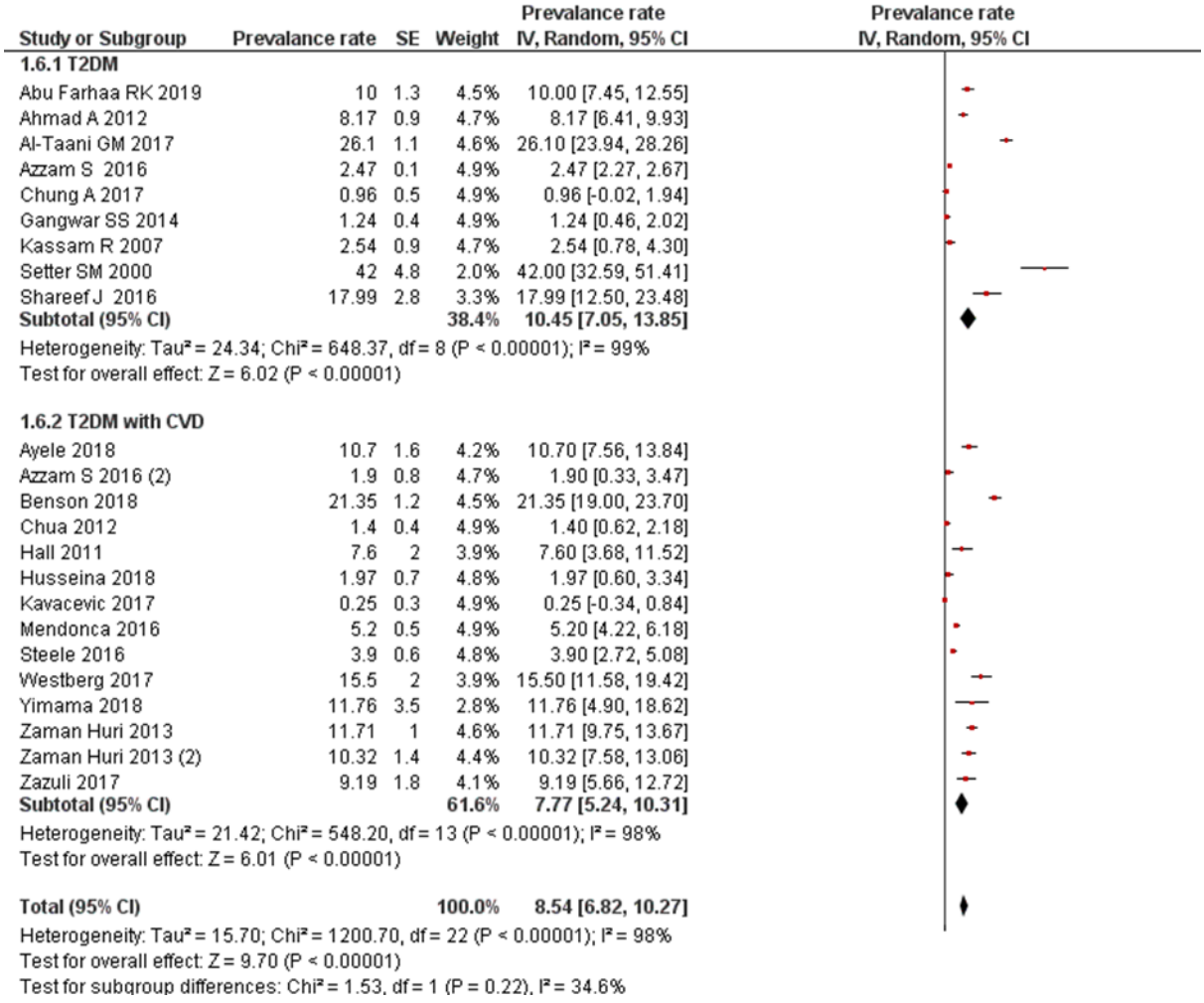

Figure 9. Funnel plot