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REVIEW ARTICLE

The association of metabolic syndrome and long acting injectable antipsychotics: A systematic review

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Abstract
Background and Objectives: Long-acting injectable (LAI) antipsychotics increase patient adherence, reduce relapse rates and facilitate regular interaction with community mental health teams. Antipsychotics are however associated with adverse effects including metabolic syndrome. This review outlines the rates of monitoring for and rates of metabolic syndrome in patients treated with LAI antipsychotics.
Methods: We searched Medline, EMBASE, and Cochrane for Medical Subject Heading (MeSH) terms including metabolic syndrome or MetS and depot or LAI antipsychotics. We included data regarding participants' clinical characteristics, dose and type of antipsychotics administered, rates of monitoring for- and rates of metabolic syndrome and individual metabolic parameters (body mass index or measure of central obesity, blood pressure, lipid levels, plasma glucose and/or HbA1C levels).
Results: Six studies were included that evaluated rates of monitoring for- and 39 studies examined rates of metabolic syndrome or individual metabolic parameters. Metabolic parameters were not routinely measured in approximately 75% of patients. Rates of metabolic syndrome ranged between 24.3% and 53.2%, with most studies finding no significant differences between oral and LAIs; however, a more preferable weight and lipid profile was detected with LAIs compared to the oral antipsychotics olanzapine and clozapine. Rates of metabolic syndrome and abnormalities of metabolic parameters were comparable among first- and second-generation and between second-generation LAIs.
Conclusions: LAI antipsychotics are associated with high rates of metabolic syndrome but low rates of regular monitoring. A robust screening plan to monitor for metabolic syndrome in individuals treated with LAIs is advised including measurement of individual metabolic parameters.

Abbreviation: LAI, Long-acting injectable; MetS, metabolic syndrome; FGA, first-generation antipsychotics; SGA, second-generation antipsychotics.

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Introduction

Long-acting injectable (LAI) or depot antipsychotics were introduced initially in the 1960s to offer an alternative treatment pathway for individuals experiencing psychotic disorders and have been associated with significant benefits in relation to relapse prevention,[1-3] and associated reduced healthcare costs.[4] LAIs provide several putative benefits compared to oral antipsychotics including consistent bioavailability resultant from avoiding first-pass effects of the liver,[5] more stable blood levels and predictable medication adherence allowing potentially use of lower total antipsychotic dosages and reduced incidences of adverse events.[6] LAI antipsychotics include both first-generation (FGAs) (flupenthixol decanoate, zuclopenthixol decanoate, pipotiazine, fluphenazine decanoate, haloperidol decanoate) and second-generation antipsychotics (SGAs) (risperidone, paliperidone, olanzapine pamoate, aripiprazole) with LAI antipsychotic administration varying between 1 and 12 weeks depending on the medication prescribed.

Individuals with schizophrenia have a 13-15 year shorter life expectancy than healthy controls, with causes of this predominantly related to the co-morbid presence of chronic physical conditions including coronary heart disease and type 2 diabetes.[7-9] Antipsychotic medications, and in particular SGAs have been associated with an increased rate of both cardiovascular side-effects and type 2 diabetes mellitus,[10] and despite a pre-existing metabolic risk for individuals diagnosed with schizophrenia, antipsychotic medications have now consistently been associated with causing metabolic dysregulation.[11,12] Metabolic syndrome is the collective term used to describe a cluster of medical parameters including central and abdominal obesity, dyslipidemias, glucose intolerance, and hypertension,[13] resulting in an increased likelihood of heart disease, type 2 diabetes, and cerebrovascular accidents.[14] Although, overall rates of metabolic syndrome are increasing[15]; a large discrepancy exists between the rates of metabolic syndrome in the general adult population compared to a population of patients diagnosed with major mental health disorders.[16] Some SGAs, including clozapine (approximately 30% after 10 years of treatment) have been particularly associated with metabolic dysregulation and high rates of metabolic syndrome.[17] FGAs have additionally been associated with this increased rates of metabolic dysregulation and metabolic syndrome, however, fewer studies have explored this association.[18] Fewer studies again have examined the impact of LAIs in relation to the risk of metabolic syndrome, despite the regular opportunity to monitor for physical health parameters on occasions when LAI antipsychotics are being administered by a clinician.[19,20]

A recent study conducted in the west of Ireland noted comparable rates of metabolic syndrome including various metabolic parameters across individuals treated with LAI antipsychotics and clozapine[21]; however, this study was not sufficiently powered to ascertain if particular LAIs were associated with differential rates of metabolic syndrome. Consequently, in this systematic review, we wanted to ascertain rates of monitoring for- and rates of metabolic syndrome in individuals prescribed LAI antipsychotics.

Materials and methods

Search strategy

A systematic bibliographical search of relevant databases (Medline, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL)) was conducted between January 1st, 1970 and December 31st, 2020 without language restriction to identify suitable studies pertaining to LAIs and metabolic syndrome. Medical Subject Heading (MeSH) keywords were: metabolic syndrome OR MetS AND depot antipsychotic OR LAI with individual LAIs additionally examined. Full texts of articles were retrieved as necessary with references reviewed to identify additional potential studies (Fig. 1).

Selection criteria

After a preliminary screen (title and abstract) to exclude studies that did not meet eligibility criteria, two of the authors (KTTN and BH) reviewed the full text of all potentially eligible studies to determine suitability for inclusion (Fig. 1). Consensus in relation to agreed study inclusion was attained from all authors. Studies were excluded if they did not include rates of metabolic syndrome or data on individual metabolic parameters.

Data extraction

Two reviewers (KTTN and BH) independently assessed and extracted relevant data including participants' clinical characteristics, the dose and type of agent administered, rates of monitoring of metabolic syndrome, rates of metabolic syndrome including levels of individual metabolic parameters (blood pressure, body mass index or measure of central obesity, lipid levels, glucose and/or HbA1C levels).

Results

Monitoring for metabolic syndrome

Five studies including two cross-sectional,[21,22] and three interrupted time series,[23-25] examined rates of monitoring of metabolic syndrome and individual metabolic parameters in patients treated with LAIs with a further cross-sectional study,[26] examining rates of monitoring for some individual metabolic parameters (see Table 1). All studies demonstrated low initial monitoring of metabolic syndrome ($\leq$ 24.1%, range 1.6%-24.1%), however, one small study (n = 23) demonstrated a rate of 60.9% at a 4-month follow-up assessment (compared to 3.9% at baseline).[25] The rates of monitoring for individual metabolic parameters were also low, with baseline assessments less than 58% for all parameters, and particularly low rates evident for the monitoring of individuals' weight (1.6%-24.1%). Two studies demonstrated significant increases in monitoring of all metabolic parameters and of metabolic syndrome on follow-up assessments (see Table 1).[23,25]

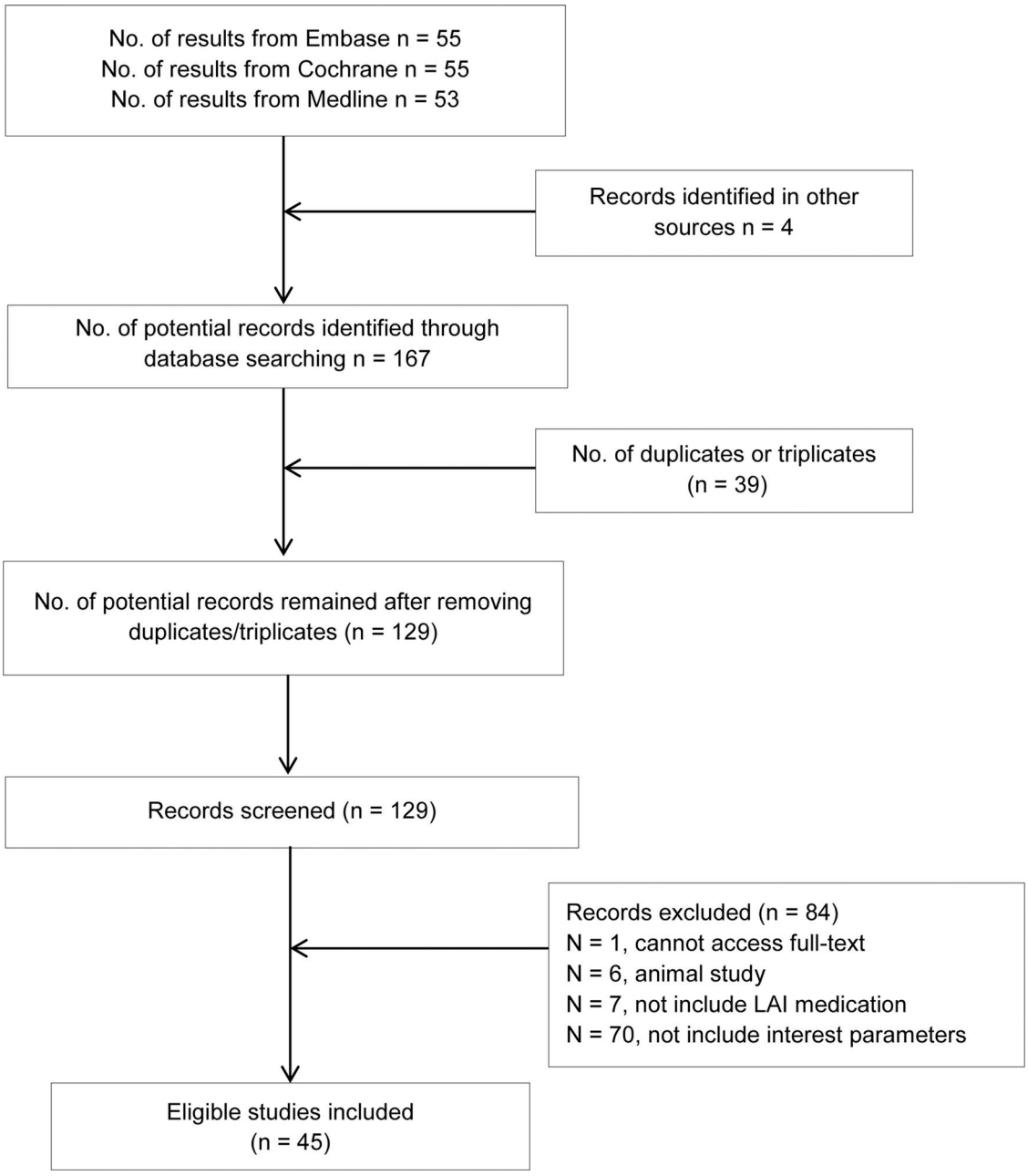

Fig. 1 Summary of study selection.

Rates of metabolic syndrome

The rates of metabolic syndrome ranged between 24.3% and 53.2% (see Table 2). Three cross-sectional studies evaluated rates of metabolic syndrome but did not compare rates between different groups of antipsychotics.[27-29] Two studies compared the rates of metabolic syndrome between oral and LAI antipsychotics, with no significant differences in metabolic syndrome rates detected.[21,30] Similarly, two studies compared different LAI antipsychotic agents (olanzapine compared to risperidone and FGAs versus SGAs) and detected no significant differences in the rates of metabolic syndrome.[31,32] Two prospective studies examined rates of metabolic syndrome at baseline and 12 months following LAI antipsychotic treatment commencement, with increased rates (15.9% v. 24.3%) demonstrated with flupenthixol,[33] and marginally reduced rates (33.3% v. 29.5%) demonstrated with paliperidone.[34] Despite this reduction in metabolic syndrome with paliperidone, an increased body mass index (BMI) (26.3 ± 6.0 kg/m^2 v. 27.1 ± 4.6 kg/m^2, $p = 0.031$) and waist circumference (98.2 ± 17.9 cm v. 101.1 ± 16.2 cm, $p = 0.021$) were demonstrated after 12 months of treatment.[34] A further four studies attained measures for all metabolic parameters but did not specifically detail the rates of metabolic syndrome in their participants.[35-38]

Individual metabolic parameters

Blood pressure (or rates of hypertension) was less frequently examined (6 studies) compared to weight, glucose, and lipid

Table 1 Studies examining rates of monitoring for metabolic syndrome.

Author	N	Screening (%)				
		MetS	Blood Pressure	Weight	Glucose Tolerance	Lipids
Barnes et al. (2007)	1966	11.0	26.3	17.3	28.4	21.8
O'Callaghan et al. (2011)						
Baseline	64	1.6	4.7	1.6	15.6	12.5
6 month follow-up	54	20.4	55.6	61.1	27.8	24.1
Cleary et al. (2012)	60	-	< 50.0	53.3	-	58.3
Najim and Islam (2013)						
Baseline	65	< 6.2	21.5	10.8	29.2	6.2
6 month follow-up		2.0	-	1.5	29.2	3.1
Gill et al. (2016)						
Baseline	23	3.9	3.9	3.9	8.7	8.7
2 month follow-up		56.5	91.3	91.3	39.1	39.1
4 month follow-up		60.9	95.7	95.7	60.9	60.9
Lydon et al. (2020)	116	24.1	38.8	24.1	40.5	44.8

MetS = Metabolic Syndrome

levels (23-29 studies). A total of 30 studies (excluding those examining metabolic syndrome (see Table 2)) investigated at least one of those four metabolic parameters (8 studies compared LAIs with baseline measurements (Table 3),[35,39-45] 4 studies compared LAIs with placebo (Table 4),[46-49] 3 studies compared LAIs with clozapine (Table 5),[50-52] 8 studies compared LAIs with other SGA oral antipsychotics (Table 5),[36,37,53-58] and 7 studies compared LAIs against other LAIs (Table 6).[38,59-64] Each study presented the measurements of individual metabolic parameters in different formats including actual data for a parameter, changes in metabolic parameter(s) over time, or rates of meeting diagnostic criteria for disorders (i.e. obesity, hypertension, diabetes mellitus, or lipid dyscrasia). There were no studies

Table 2 Studies examining rates of metabolic syndrome.

Author	Treatment	N	Metabolic Syndrome%	p
Cross-sectional studies				
Dehelean et al. (2015)[28]	LAI olanzapine + risperidone	28	39.2	-
Sanchez-Martinez et al. (2018)[28]	LAI antipsychotics	130	46.2	-
Ventriglio et al. (2019)[30]	Oral antipsychotics: risperidone, haloperidol, olanzapine, aripiprazole, quetiapine, paliperidone, clozapine, ziprasidone	64	32.1	ns
	LAI antipsychotics: paliperidone, risperidone, aripiprazole, olanzapine	87	31.6	
Dehelean et al. (2019),[32]	LAI olanzapine	41	53.2	ns
	LAI risperidone	36	46.8	
Morell et al. (2019),[27]	LAI antipsychotics (FGA and SGA)	301	43.9	-
Lydon et al. (2020),[21,*]	Clozapine	119	38.9	ns
	LAI antipsychotics	116	31.1	
Molteni et al. (2020),[31]	FGA LAI: haloperidol, zuclopenthixol, fluphenazine	84	36.9	ns
	SGA LAI: aripiprazole, risperidone, paliperidone	36	25.8	
Longitudinal studies				
Chiliza et al. (2015),[33]	LAI flupenthixol			
	Baseline	107	15.9	No p value provided
	After 12 months		24.3	
Rosso et al. (2016),[34]	LAI paliperidone			ns
	Baseline	60	33.3	
	After 12 months		29.5	

[*] Lydon et al., (2020) is additionally presented in Table 1, as it also examined the rate of monitoring for metabolic syndrome.

Table 3 Studies examining individual metabolic parameters of LAI antipsychotics.

Author	Study design	Treatments	Weight	Blood pressure	Glucose level	Lipid levels
Prevalence of metabolic abnormalities (%)			*Weight gain*	*Hypertension*	*Diabetes*	*Dyslipidemia*
Wildin et al. (2013),[35]	Cross-sectional	LAI antipsychotics: risperidone, fluphenazine, haloperidol, clopentixol, flupenthixol (N =37)	86.4%	22.0%	21.6%	72.9%
Incidence of metabolic abnormalities (% new cases diagnosed)			*Weight gain*	*Hypertension*	*Diabetes*	*Dyslipidemia*
Rosa et al. (2012),[39]	Single-arm trial Duration 6 months	LAI risperidone (switched from oral olanzapine ≥ 4 weeks) (N = 96)	22.7%	-	1.0%	2.1%
Sliwa et al. (2014),[40]	Single-arm trial	LAI paliperidone (N = 644)				
	Duration 204 days	Normal weight patients	11.4%	-	2.2%	2.6%
		Overweight patients	7.3%	-	3.9%	1.3%
		Obese patients	11.7%	-	4.6%	4.6%
Zhao et al. (2017),[41]	Single-arm trial Duration 25 weeks	LAI paliperidone (N = 353)	28.6%	-	0.6%	1.1%
Gonzales-Garrido et al. (2017),[42]	Cross-sectional	LAI paliperidone (N =89)	-	13.4%	9.0%	10.1%
Change in metabolic parameter level			*Weight (SD) (kg)*	*Blood pressure (SD) (mmHg)*	*Fasting glucose (SD) (mmol/L)*	*Lipid (SD) (mmol/L)*
Mc Donell et al. (2014),[43]	Single-arm trial Duration: 6 years	LAI olanzapine (N = 393)	+2.1 (7.8) $p < 0.001$	-	+0.3 (1.6) $p < 0.001$	TC: +0.1 (0.95) $p = 0.128$
Anand et al. (2015),[44]	Longitudinal Duration 6 years	LAI olanzapine (N = 669)	+2.2 (8.0) $p < 0.001$	-	+0.3 (1.6) $p < 0.001$	TC: 0.1 (1.0) $p = 0.073$
Nasrallah et al. (2017),[45]	Single-arm trial Duration 52 weeks	LAI aripiprazole (N = 478)	+0.8 (5.9) ns	-	+0.1 (1.5) ns	TC: -0.1 (2.6) ns

SD = standard deviation; ns = not significant
TC = total cholesterol

Table 4 Studies comparing LAIs v. placebo in relation to individual metabolic parameters.

Author	Study Design	Treatments	Weight gain	Blood Pressure	Diabetes	Dyslipidemia
Pandina et al. (2010),[47]	RCT	LAI paliperidone 25 mg (N = 160)	5.6%	-	-	-
		LAI paliperidone 100 mg (N = 165)	7.9%	-	-	-
		LAI paliperidone 150 mg (N = 163)	12.9%	-	-	-
		Placebo (N = 164)	4.9%	-	-	-
		Duration 13 weeks	$p < 0.05$			
Nasrallah et al. (2010),[48]	RCT	LAI paliperidone 25 mg (N = 130)	↑Weight (SD): 0.4 (4.0) kg	-	-	-
		LAI paliperidone 50 mg (N = 128)	↑Weight (SD) 0.8 (3.3) kg	-	-	-
		LAI paliperidone 100 mg (N = 131)	↑Weight (SD) 1.3 (3.4) kg	-	-	-
		Placebo (N = 125)	↑Weight (SD) −0.5 (4.8) kg	-	-	-
		Duration 13 weeks	NS			
Kramer et al. (2010),[46]	RCT	LAI paliperidone 50mg (N = 79)	↑Weight (SD): 0.7 (2.71) kg	-	1.3%	-
		LAI paliperidone 100mg (N = 84)	↑Weight (SD): 1.4 (3.49) kg	-	0%	-
		Placebo (N = 84)	↑Weight (SD): -0.3 (2.99)	-	0%	-
		Duration 9 weeks	$p < 0.001$		ns	
Calabrese *et al*. (2018),[49]	RCT	LAI aripiprazole (N =133)	13.3%	-	4.3%	11.9%
		Placebo (N =133)	12.1%	-	5.5%	13.5%
			($p > 0.05$)		($p > 0.05$)	($p > 0.05$)

RCT =Randomised Controlled Trial; SD =standard deviation; ns = not significant
TC =total cholesterol
Weight gain: having body weight increase ≥ 7%

Table 5 Studies compared LAIs and SGAs in relation to individual metabolic parameters.

Author	Study design	Treatments	Weight	Hyper-tension	Diabetes	Dys-lipidemia
LAIs compared to clozapine						
Hägg et al. (1998),[50]	Cross-Sectional	Clozapine (N = 63)	-	-	Prevalence 21.7%	-
		LAIs (N = 67)	-	-	Prevalence =9.5% p = 0.06	-
Miller and Molla (2005),[51]	Retrospective	Clozapine (N =24) Mean duration: 64 months	-	-	27.7% new cases (20.8% pre-existing)	-
		LAIs (N =27) (fluphenazine = 18; haloperidol = 9) Mean duration: 98 months	-	-	0% new cases (19.0% pre-existing)	-
					no p value provided	
Martínez-Andrés and García-Carmona (2020),[52]	Retrospective	Clozapine (N = 33) Mean duration: 4.01 years	BMI 27.8 ± 1.0 kg/m^2	-	FPG: 85.6 ± 3.4 mg/dL	TC: 146.3 ± 5.3 mg/dL
		Switched from clozapine to LAI paliperidone (N =33) Mean duration: 4.37 years	BMI: 25.8 ± 0.9 kg/m^2	-	FPG: 77.2 ± 2.3 mg/dL	TC: 135.2 ± 5.6 mg/dL
			p = 0.01		p < 0.01	p = 0.02
LAIs compared to other SGAs						
MacFadden et al. (2010),[53]	RCT	LAI risperidone (N = 179)	↑Weight (SD): +2.6 (5.8) kg	-	↑FPG (SD): +0.3 (1.7) mmol/L	↑TC (SD) : -0.1 (0.8) mmol/L
		Oral aripiprazole (N = 176)	↑Weight (SD): +1.6 (7.7) kg	-	↑FPG (SD): -0.2 (1.6) mmol/L	↑TC (SD): -0.3 (0.8) mmol/L
		Duration 2 years	ns		ns	ns
Chengapa et al (2010),[54]	RCT	LAI risperidone (N =23)	Incidence of weight gain: 38.1%	-	-	-
		Oral antipsychotics (N=25) (aripiprazole = 11, quetiapine = 8, olanzapine = 5, ziprasidone = 1)	Incidence of weight gain: 50.0%	-	-	-
		Duration: 15 months	ns			
McDonnell et al. (2011),[55]	RCT	LAI olanzapine (N =599)	↑BMI (SD): +0.5 (1.4) kg/m^2	-	↑FPG (SD): +1.3 (16.2) mg/dL	↑TC (SD): -2.3 (28.0) mg/dL
		Oral olanzapine (N =322)	↑BMI (SD): +0.4 (1.4) kg/m^2	-	↑FPG (SD): +3.1 (23.1) mg/dL	↑TC (SD): -6.0 (32.8) mg/dL
		Duration: 24 weeks	p = 0.33		p = 0.17	p = 0.17
Fleischhacker et al. (2014),[58]	RCT	Oral aripiprazole (10-30 mg/day) (N = 266)	↑Weight (SD): +1.0 kg (4.8)	-	↑FPG (SD): -1.07 (19.06) mg/dL	↑TC (SD): -3.89 (27.15) mg/dL
		LAI aripiprazole 50 mg (N = 131)	↑Weight (SD): -1.6 kg (7.4)	-	↑FPG (SD): 0.19 (30.36) mg/dL	↑TC (SD): -4.56 (28.29) mg/dL
		LAI aripiprazole 400 mg (N = 265)	↑Weight (SD): +0.1 kg (4.8)	-	↑FPG (SD) 1.65 (31.31) mg/dL	↑TC (SD): -0.38 (26.46) mg/dL
		Duration 38 weeks	p < 0.05		ns	ns
Subotnik al. (2015),[36]	RCT	LAI risperidone (N = 40)	BMI: 30.8 ± 6.1 kg/m^2	SBP/DBP 119.2 ± 11.4/ 75.9 ± 7.1 mmHg	HbA1c: 5.7 ± 1.3%	TC: 177.9 ± 6.6 mg/dL
		Oral risperidone (N = 43)	BMI: 28.3 ± 6.7 kg/m^2	SBP/DBP 117.2 ± 11.6/ 72.5 ± 11.5 mmHg	HbA1c: 5.3 ± 0.3%	TC: 171.9 ± 7.0 mg/dL
		Duration 12 months	ns	ns	ns	ns
	Cross-sectional	LAI risperidone or paliperidone (N = 39)	WC: 90.2 ± 12.0 cm	SBP: 120 (100 - 140) DBP: 80 (60 - 90) mmHg	FPG 91.8 ± 19.2 mg/dL	TG 131 ± 57.8 mg/dL

Table 5 (*Continued*)

Author	Study design	Treatments	Weight	Hyper-tension	Diabetes	Dys-lipidemia
Sağlam Aykut and Özkorumak Karagüzel (2018),[37]		Oral SGA (N =124): quetiapine, olanzapine, paliperidol, aripiprazole, risperidone, amisulpride, clozapine	WC: 96.7 ± 15.6 cm	SBP: 120 (90 - 170) DBP: 80 (60 - 90) mmHg	FPG 90.00 ± 14.168 mg/dL	TG: 168.3 ± 90.5 mg/dL
			p = 0.02	p > 0.05	p = 0.53	p = 0.003
Huang et al. (2018),[56]	RCT	LAI paliperidone (N =28)	WC: 80.5 ± 9.0 cm	-	FPG: 4.9 ± 0.4 mmol/L	TC: 4.0 ± 0.8 mmol/L
		Oral olanzapine (N =29)	WC: 80.1 ± 8.3 cm	-	FPG: 5.2 ± 0.6 mmol/L	TC: 4.7 ± 1.1 mmol/L
		Duration 13 weeks	p = 0.05		p = 0.57	p = 0.01
Keks et al. (2018),[57]	RCT	LAI risperidone (N = 247)	↑Weight: +1.7 kg	-	Incidence of diabetes: 2%	-
		Oral olanzapine (N = 300)	↑Weight: +4.0 kg	-	Incidence of diabetes: 2%	-
		Duration 12 months	p < 0.05		ns	

RCT = Randomised Controlled Trial; SD =standard deviation; ns = not significant
SBP = systolic blood pressure; DBP =diastolic blood pressure; WC = waist circumference
FPG =fasting plasma glucose; TC = total cholesterol; TG= triglyceride

that compared individual FGA LAIs with each other for any metabolic parameter.

LAIs were associated with weight gain which was demonstrated in 37.3%-86.4% of patients.[21,27,32,35] Diabetes mellitus were diagnosed in 21.6%-51.7% of patients taking LAI antipsychotics,[21,27,32,35] with 0.6%-9% of individuals developing diabetes mellitus, and up to 29.7% of patients developing impaired glucose tolerance after commencement of LAI antipsychotics.[35,41-43] The prevalence of hypertension in patients treated with LAIs was 21.6%-62.1%.[27,32,34,35] Dyslipidaemia was noted in 40.5%-72.9% of patients, 3.3% of patients had their cholesterol level changed from normal to high, and 9.3% of patients had their triglyceride level changed from normal to high with LAI antipsychotic treatment (see Table 3).[21,27,32,35,43] Nevertheless, randomized controlled trials found mixed results regarding the increased risk of metabolic abnormalities.

Compared to placebo, the LAI antipsychotic aripiprazole was not associated with an increase in the incidences of diabetes (4.3% v. 5.5%) or lipid dysregulation (11.9% v. 13.5%) after 52 weeks.[49] Two studies demonstrated an association between the LAI antipsychotic paliperidone and weight gain, with either an increased body weight compared to placebo (+0.7 ± 2.71 kg v. -0.3 ± 2.99 kg, $p < 0.001$),[46] or a higher proportion gaining more than 7% of their weight compared to placebo (13% v. 6%, $p < 0.05$).[47] In contrast, one study detected no statistical significance in weight gain for paliperidone compared to placebo over a 13 week period (+1.3 ± 3.35 kg v. −0.5 ± 4.83 kg).[48]

Comparison of LAIs with oral antipsychotic medications

LAIs when compared to clozapine demonstrated reduced BMI (25.8 ± 0.9 kg/m^2 v. 27.8 ± 0.1 kg/m^2, p = 0.01),[52] or reduced rates of obesity (37.3% v. 50.0%, p = 0.18).[21] A reduced total cholesterol level (135.2 ± 5.6 mg/dL v. 146.3 ± 5.3 mg/dL, p = 0.02) was demonstrated with the LAI antipsychotic paliperidone compared to clozapine.[52] LAIs were associated with reduced fasting glucose levels (77.2 ± 2.3 mg/dL v. 85.6 ± 3.4 mg/dL, $p < 0.01$),[52] reduced rates of new-onset- (0% v. 27%),[51] or prevalence of diabetes (10% v. 22%, p = 0.06),[50] compared to clozapine (see Table 5).

LAIs compared to other SGA oral medications predominantly revealed similar findings relating to different metabolic parameters[36,37,53-58] (see Table 5). Most studies found no significant differences between LAIs and SGA oral medications.[53-55] Three studies demonstrated a more preferable weight and lipid profile of LAIs.[37,56,58] Risperidone or paliperidone LAI compared to oral antipsychotics including olanzapine and clozapine demonstrated reduced central obesity (waist circumference 90.2 ± 12.0 cm v. 96.7 ± 15.6 cm, p = 0.02),[37] and were associated with less weight gain compared to patients treated solely with oral olanzapine (+1.7kg v. +4.0kg, $p < 0.05$).[57] Fleischhacker et al. demonstrated marginal weight gain with oral aripiprazole (+1 ± 4.8 kg) compared to a marginal weight reduction with 50 mg aripiprazole LAI (-1.6 ± 7.4 kg, $p < 0.05$); however the LAI dose employed was a sub-clinical treatment dose and no significant difference were evident in weight with a standard clinical dose of 400mg (+1 ± 4.8 kg).[58] Regarding lipid profiles, the LAI antipsychotic paliperidone was less likely to increase

Table 6 Studies comparing individual LAIs in relation to different metabolic parameters.

Author	Treatments	Weight gain	Hypertension	Diabetes	Dyslipidemia
Gopal et al (2011),[63]	52 weeks paliperidone treatment after: Maintenance phase (N = 74)	Incidence 9.5%	-	Incidence 1.6%	Incidence 1.6%
	Maintenance phase and 18 weeks placebo (N = 153)	Incidence 7.2%	-	Incidence 0.7%	Incidence 2.1%
	Maintenance phase and 24 weeks paliperidone (N = 161) (maintenance phase: 24 weeks with paliperidone)	Incidence 4.3% ns	-	Incidence 1.3% ns	Incidence 0.7% ns
Hill et al. (2011),[64]	Olanzapine				
	Low dose: 150 mg/2 weeks (N = 140)	↑Weight (SD): +0.7 (4.4) kg	-	-	Incidence of increased TG 3.2%
	Medium dose: 405 mg/4 weeks (N = 318)	↑Weight (SD): +0.9 (3.9) kg	-	-	Incidence of increased TG 6.0%
	High dose: 300 mg/2 weeks (N = 141)	↑Weight (SD): +1.70 (4.1) kg	-	-	Incidence of increased TG 18.9%
	Duration: 24 weeks	p = 0.024			p = 0.001
Covell et al. (2012),[62]	Fluphenazine / Haloperidol (N = 30)	↑BMI (SD): −0.3 (1.7) kg/m^2	-	-	-
	Risperidone (N = 32)	↑BMI (SD): + 1.0 (2.0) kg/m^2	-	-	-
	Duration: 12 months	p = 0.65			
Fu et al. (2014),[60]	Paliperidone (N = 161)	↑Weight (SD): + 1.62 (0.4) kg	-	↑FPG (SD): +7.16 (2.15) mmol/L	↑LDL-C (SD): +0.11 (1.48) mmol/L
	Risperidone (N=173)	↑Weight (SD): + 1.53 (0.4) kg	-	↑FPG (SD): +5.34 (2.12) mmol/L	↑LDL-C (SD): +3.2 (1.5) mmol/L
	Duration: 13 weeks	ns		ns	p = 0.023
McEvoy et al. (2014),[61]	Haloperidol (N =154)	↑Weight: −3.88 (−7.02 to −0.73) kg	-	↑FPG: +20.96 (12.38 - 29.54) mg/dL	↑LDL-C: +13.49 (8.85 - 18.14) mg/dL
	Paliperidone (N =157)	↑Weight: +6.04 (2.88 - 9.20) kg	-	↑FPG: +21.13 (12.59 - 29.67) mg/dL	↑LDL-C: +11.70 (7.06 - 16.34) mg/dL
	Duration: 24 months	p < 0.001		p = 0.98	p = 0.59

Table 6 (*Continued*)

Author	Treatments	Weight gain	Hypertension	Diabetes	Dyslipidemia
Savitz et al (2016),[38]	Paliperidone Monthly (N = 512)	Incidence 16.4%	Incidence 1.4%	↑FPG (SD): 0.086 (0.95) mmol/L	↑TC (SD): 0.043 (0.72) mmol/L
	3 Monthly (N = 504)	Incidence 15.2%	Incidence 2.4%	↑FPG (SD): -0.004 (1.02) mmol/L	↑TC (SD): 0.034 (0.74) mmol/L
	Duration: 48 weeks	ns	ns	ns	ns
Shymko et al. (2020),[59]	Aripiprazole (N = 33)	Incidence 30.0%	-	-	TG: 1.35 (1.27 - 1.42) mmol/L
	Paliperidone (N = 26)	Incidence 26.9%	-	-	TG: 1.89 (1.82 - 1.96) mmol/L
	Duration: 12 months	p = 0.77			p < 0.01

FPG= fasting plasma glucose; SD = standard deviation TG = triglyceride; Weight gain: having body weight increase ≥ 7%

total cholesterol compared to olanzapine orally (4.0 ± 0.8 mmol/L v. 4.7 ± 1.1 mmol/L, p = 0.011)[56] with both risperidone or paliperidone LAIs demonstrating lower triglyceride levels compared to patients treated with oral olanzapine or clozapine (131 ± 57.8 mg/dL v. 168.3 ± 90.5 mg/dL, p = 0.003).[37]

Comparison between individual LAIs

A comparison between different LAIs demonstrated similar findings[38,59,60,62-64] (see Table 6); however, some differences in metabolic parameters between individual LAIs were noted. A weight reduction of 3.88kg (95% CI, -7.02 to -0.73) with haloperidol compared to an increase of 6.04 kg (95% CI, 2.88 to 9.20) with paliperidone over 24 months was noted in one study.[61] Higher doses of olanzapine were associated with more significant increases in body weight (1.7 ± 4.1 kg v. 0.7 ± 4.4 kg, p = 0.02) and higher rates of elevated triglyceride level (18.9% v. 3.2%, p = 0.01) over 24 weeks.[64] A longer treatment duration or longer administration interval of paliperidone was not associated with increased or reduced rates of abnormalities for any metabolic parameter.[38,63] Paliperidone was associated with increased triglyceride levels compared to aripiprazole (1.89 (95% CI 1.82-1.96) mmol/dL v. 1.35 (95% CI 1.25-1.42) mmol/dL, p = 0.01)[59]; however paliperidone was less likely to increase LDL cholesterol levels compared to risperidone (0.11 ± 1.48 mmol/L v. 3.2 ± 1.5 mmol/L, p = 0.023).[60] Risperidone was associated with increased rates of hypertension compared to olanzapine (62% v. 38%, p = 0.04).[32]

Discussion

This systematic review provides a comprehensive overview of previous studies conducted to identify the rates of monitoring for- and rates of metabolic syndrome in patients treated with LAI medication. Despite clear clinical and economic benefits associated with LAI antipsychotics, high rates of metabolic dysregulation are demonstrated, with poor rates of monitoring evident despite opportunities for such monitoring secondary to the mode of treatment administration.

Few studies to date, have examined rates of monitoring of metabolic syndrome in individuals treated with LAIs. These studies noting that less than a quarter of individuals treated with LAI antipsychotics were monitored for metabolic syndrome, with varying low rates of monitoring for individual metabolic parameters. More regular monitoring was however associated in two studies (O'Callaghan et al., Gill et al.) with improved monitoring for all metabolic indices after the introduction of a screening checklist or a monitoring clinic, albeit glucose and lipid level monitoring continued to be recorded at modest rates.[23,25] There are a number of putative reasons why individuals receiving LAIs are not regularly monitored for metabolic syndrome. Firstly, many participants do not have a monitoring structure for metabolic screening in place. This is in contrast to many patients treated with the antipsychotic medication clozapine where there is mandatory full blood count monitoring.[21] This monitoring structure provides an opportunity to regularly and consistently monitor patients for a variety of

health conditions including metabolic parameters. Secondly, many patients treated with LAIs, due to the nature of their illness and associated negative and cognitive symptoms, do not prioritize management of their physical health and thus may not attend primary care in a timely fashion compared to the general population.[65] In addition, many patients with schizophrenia have limited awareness of the term "metabolic syndrome" or aspects of their diets that might increase the risk of metabolic syndrome and thus may not prioritize routine monitoring of their physical health[66] Early recognition of abnormal metabolic parameters allows for early intervention, improving long-term cardiovascular outcomes. Interventions addressing dietary intake and levels of activity during LAI visits (or clinics) would also likely be an effective intervention to combat premature morbidity secondary to abnormal metabolic parameters. This is particularly important as many individuals diagnosed with metabolic syndrome are asymptomatic.[67]

The rates of metabolic syndrome for individuals treated with LAI ranged approximately from one-quarter to a half of participants treated with LAIs, with broadly similar rates noted for both FGAs and SGAs and similar rates between LAIs and oral antipsychotics. Studies assessing rates of metabolic syndrome have largely been cross-sectional and thus cannot definitively determine what percentage of individuals developed metabolic syndrome secondary to the initiation of LAIs; however, a significant role for LAIs as a causative factor for metabolic syndrome is strongly suggested.

A larger number of studies have evaluated individual metabolic parameters and have included both cross-sectional and prospective studies (including some as components of randomized controlled trials). These studies have noted heterogeneous results. Most studies have demonstrated no significant differences between the rates of metabolic abnormalities with LAI and oral formulation, except for olanzapine and in particular clozapine. Clozapine was associated with a significantly higher risk of weight gain, impaired glucose tolerance, and increased lipid levels compared with LAIs[50,52]; albeit this was not a universal finding.[21] Of note, clozapine is associated with increased metabolic dysregulation compared to several other antipsychotics in oral formulation.[68,69] Whilst some studies noted a more favourable metabolic profile with LAI antipsychotics, the probable increased risk of metabolic dysregulation associated with some comparator antipsychotic medications including clozapine and olanzapine are likely causative for these positive findings.[37,56,58]

Most head-to-head studies that compared specific individual LAI antipsychotics found comparable rates of metabolic abnormalities and minimal differences in individual metabolic parameters of clinical importance. We do not infer that all individual LAI antipsychotics are equivalent, and future well-powered studies comparing a range of LAIs are required to delineate out the individual risk of metabolic syndrome across LAI antipsychotics. Nevertheless, this systematic review notes high rates of metabolic dysregulation in patients treated with a range of LAI antipsychotic medications, with particularly high levels of weight gain and lipid dysregulation evident. Consequently, routine metabolic monitoring for patients treated with LAI antipsychotic medications is required and likely feasible at the time of delivery of the LAI.

Conclusions

This systematic review demonstrates low rates of monitoring patients taking LAI antipsychotic medications for metabolic syndrome including individual metabolic parameters, despite LAIs demonstrating predominantly similar rates of metabolic syndrome to oral SGAs with opportunities afforded for such monitoring given the regular clinician contact for LAI administration. A robust screening plan for metabolic syndrome, encompassing measurement of body weight and waist circumference, blood pressure, fasting glucose and lipid levels, is required in individuals treated with LAIs given the significant potential of developing cardiovascular disease and metabolic syndrome. Regular auditing of monitoring rates for metabolic syndrome and individual parameters for individuals treated with LAIs would also likely improve rates of monitoring.

Ethical considerations

Ethical approval was attained from the Galway University Hospitals Research Ethics Committee (C.A. 2723) for this study. Additionally, each study included in the systematic review had attained ethics committee approval from their individual local research ethics committees.

Declaration of competing interest

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