Salute fisica e salute mentale, associazione o causalità?

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Background

- People with severe mental illness (SMI) have excess mortality, being 2 to 3 times higher compared to the general population
- 60% of this excess mortality is due to physical illness
- Physical illnesses are more prevalent and have a greater impact in SMI patients
- Several factors contribute to the poor physical health of SMI patients:
  - individual lifestyle choices
  - disparities in health care access, utilization and provision

Physical illnesses with increased frequency in SMI patients

Bacterial infections and mycoses	Tuberculosis (+)
Viral diseases	HIV (++), hepatitis B/C (+)
Neoplasms	Obesity-related cancer (+)
Musculoskeletal diseases	Osteoporosis/decreased bone mineral density (+)
Stomatognathic diseases	Poor dental status (+)
Respiratory tract diseases	Impaired lung function (+)
Urological and male genital diseases	Sexual dysfunction (+)
Female genital diseases and pregnancy complications	Obstetric complications (++)
Cardiovascular diseases	Stroke, myocardial Infarction, arterial hypertension, other cardiac and vascular diseases (++)
Nutritional and metabolic diseases	Obesity (++), diabetes mellitus (+), metabolic syndrome (++), hyperlipidemia (++)

(++) very good evidence and (+) good evidence for increased risk

Adapted from Leucht et al. (Acta Psychiatr Scand 2007; 116:317-333).

Impact of SMI on physical health

MEDICAL CONDITION	RELATIVE RISK
Type 2 diabetes	> 3
Dyslipidemia	> 3
Respiratory difficulties	> 3
Cardiovascular disease	> 2-3
Hypertension	> 2-3
Reproductive hormone abnormalities	> 1-2
Certain cancers (e.g. colon)	> 1-2

Adapted from Holt and Peveler (Diabetes Obes Metab 2009;11:665-679).

Assessment of overweight and obesity

- Body mass index (BMI) (kg/m^2)
  - BMI $\geq$ 25 kg/m^2 (Asian BMI $\geq$ 23 kg/m^2) = overweight
  - BMI $\geq$ 30 kg/m^2 (Asian BMI $\geq$ 25 kg/m^2) = obesity
- Waist circumference (WC)
  - measuring abdominal or central adiposity
  - more valid and reliable predictor than BMI of risk for type 2 diabetes, cardiovascular disease and other metabolic-related conditions
  - lower cutoff points for Asians

Ethnicity-specific WC cutoff values

	Europids, Sub-Saharan Africans, Mediterranean and Middle Eastern populations	South Asians, Chinese, and ethnic South and Central Americans	Japanese	Northern Americans
Men	**≥ 94 cm**	**≥ 90 cm**	**≥ 90 cm**	**≥ 102 cm**
Women	**≥ 80 cm**	**≥ 80 cm**	**≥ 82-85 cm**	**≥ 88 cm**

Adapted from Alberti et al (Circulation 2009; 120: 1640-1645).

Obesity and SMI patients

- Persons with SMI are, compared to the general population, at increased risk for overweight, obesity and abdominal obesity
  - schizophrenia
    - 2.8 to 3.5 increased likelihood of being obese
    - rates of obesity (BMI ≥ 30): 42-60% (Canadian and U.S. studies)
  - major depression or bipolar disorder
    - 1.2. to 1.5 increased likelihood of being obese
    - rates of overweight or obesity: up to 68%
- SMI obesity is associated with:
  - lifestyle factors (e.g. poor diet)
  - illness-related factors (e.g. depressive symptoms)
  - treatment-related factors (e.g. weight liability of certain psychotropic agents)

Obesity and psychotropics

- Weight gain is a well established effect of some psychotropics
  - antipsychotic treatment
    - hierarchy for risk of weight gain
    - no antipsychotic is truly weight-neutral: all antipsychotics cause significant weight gain in antipsychotic-naïve or first-episode patients
  - antidepressants and mood stabilizers
    - hierarchy for risk of weight gain
- High inter-individual variability in medication-induced weight gain suggests influence of genetic factors

Weight liability of psychotropic agents used in SMI

Drug class	Weight loss	Relatively weight neutral	Weight gain
Antidepressants	Bupropion Fluoxetine	Citalopram Duloxetine Escitalopram Nefazodone Sertraline Venlafaxine	<u>Substantial</u> Amitriptyline Imipramine Mirtazapine <u>Intermediate</u> Nortriptyline Paroxetine
Anticonvulsants/ Mood stabilizers	Topiramate Zonisamide	Lamotrigine Oxcarbazepine	<u>Substantial</u> Lithium Valproate <u>Intermediate</u> Carbamazepine Gabapentin
Antipsychotics	Aripiprazole (in pre-treated individuals) Molindone (in pre-treated individuals) Ziprasidone (in pre-treated individuals)	Amisulpride Aripiprazole Asenapine Fluphenazine Haloperidol Lurasidone Perphenazine Ziprasidone	<u>Substantial</u> Chlorpomazine Clozapine Olanzapine <u>Intermediate</u> Iloperidone Paliperidone Risperidone Quetiapine Sertindole Thioridazine Zotepine

Metabolic syndrome (MetS) in the general population

- Main characteristics
  - central obesity, hypertension, dyslipidemia, glucose intolerance or insulin resistance
- Large variations in prevalence estimates across definitions, countries or regions, gender, ethnicity, and age groups
- Relatively higher prevalence in North and South America than other regions in the world
- Associated with increased risk of developing different medical conditions
  - type 2 diabetes: 5-6-fold increased risk
  - coronary heart disease: 3-6 fold increased risk
  - certain cancers (e.g. colon cancer)

Working definitions of MetS

Criteria	WHO (1998, 1999)	EGIR (1999)	NCEP ATP III (2001, 2004)	AACE/ACE (2003)	IDF (2005)	IDF & AHA/NHLBI (2009)
Required factor	IGF, IFG or DM type 2, and/or insulin resistance **plus any 2 or more of following**	insulin resistance or hyperinsulinemia (highest 25%) **plus any 2 of following**	None **but any 3 or more of the following 5 features**	At least one of the specified risk factors (e.g. obesity, sedentary lifestyle, age > 40) **plus 2 or more of following**	Central obesity (with ethnicity-specific cutoff values) **plus any 2 of following**	None **any 3 or more of following**
Additional factors						
Obesity	Waist-to-hip ratio >0.90 (men) >0.85 (women), and/or BMI>30 kg/m^2	WC ≥ 94 cm (men) WC ≥ 80 cm (women)	WC ≥ 102 cm (men) WC ≥ 88 cm (women)	BMI>25 kg/m^2 or WC > 102 cm (men) WC > 89 cm (women) (10-15% lower for non-Caucasians)		Elevated WC (population) and country-specific definitions as defined by IDF and AHA/NHLBI until more data are available
Triglycerides **HDL-cholesterol**	≥ 150 mg/dl (≥ 1.7 mmol/L) **and/or** < 35 mg/dL(< 0.9 mmol/L) (men) < 39 mg/dL(< 1.0 mmol/L) (women)	> 177 mg/dl (> 2.0 mmol/L) < 40 mg/dL (< 1.0 mmol/L (men and women) or dyslipidemia Rx	≥ 150 mg/dl (≥ 1.7 mmol/L) or elevated triglycerides Rx < 40 mg/dL (< 1.03 mmol/L)(men) < 50 mg/dL (< 1.29 mmol/L(women) or reduced HDL-cholesterol Rx	>150 mg/dl < 40 mg/dL (men) < 50 mg/dL (women)	≥ 150 mg/dl (≥ 1.7 mmol/L) or on lipid abnormality Rx < 40 mg/dL (< 1.03 mmol/L)(men) < 50 mg/dL (< 1.29 mmol/L(women) or lipid abnormality Rx	≥ 150 mg/dl (≥ 1.7 mmol/L) (Rx for elevated triglycerides is an alternate indicator) < 40 mg/dL (< 1.0 mmol/L)(men) < 50 mg/dL (< 1.3 mmol/L(women) or lipid abnormality Rx
Blood pressure	≥ 160/90 mm Hg (later modified as ≥ 140/90 mm Hg)	≥ 140/90 mmHg or hypertension Rx	≥ 130/85 mm Hg or hypertension Rx	≥ 130/85 mm Hg	≥ 130/85 mm Hg or antihypertensive Rx	≥ 130/85 mm Hg (antihypertensive Rx in a patient with a history of hypertension is an alternate indicator)
Glucose	IGT, IGF (≥ 110 mg/dL) (≥ 6.1 mmol/L), or DM type 2	IGT or IGF (≥ 110 mg/dL) (≥ 6.1 mmol/L), (but not DM)	≥ 110 mg/dL (≥ 6.1 mmol/L), (includes DM) (later modified as ≥ 100 mg/dL) (≥ 5.6 mmol/L), or on elevated glucose Rx	100-125 mg/dl	≥ 100 mg/dL (≥ 5.6 mmol/L) or previously diagnosed type 2 DM	≥ 100 mg/dL (≥ 5.6 mmol/L) (Rx of elevated glucose is an alternate indicator)
Other	Microalbuminuria (urinary albumin excretion rate ≥ 20 µg/min or albumin: creatinine ratio ≥ 20 mg/g (later modified as ≥ 30 mg/g)					

MetS in SMI patients

- People with SMI exhibit a higher MetS prevalence than their peers in the general population across the world
  - schizophrenia: 19.4-68%
  - schizoaffective disorder: 42%
  - bipolar disorder: 22-30%
- Lifestyle and behavioural patterns (smoking, physical inactivity, dietary habits) play important roles in the prevalence of the MetS in these populations
- MetS remains underdiagnosed and undertreated among people with SMI. The proportion of patients not receiving tests for assessing metabolic risk factors is high

Approximate relative likelihood of metabolic disturbances with antipsychotic medication

Medication	Risk for MetS
Chlorpromazine	High (?, limited data)
Clozapine	High
Olanzapine	High
Quetiapine	Moderate
Amisulpride	Mild
Iloperidone	Mild (?, limited data)
Paliperidone	Mild
Risperidone	Mild
Sertindole	Mild
Aripiprazole	Low
Asenapine	Low (?, limited data)
Haloperidol	Low
Lurasidone	Low (?, limited data)
Perphenazine	Low
Ziprasidone	Low

Adapted from Hasnain et al (Curr Diab Rep 2010;10: 209-216).

Disparities in health care of MetS in SMI patients

- Even after the FDA (Food and Drug Administration) and the ADA (American Diabetes Association)/APA (American Psychiatric Association) recommendations for novel AP, the frequency of baseline glucose and lipid testing showed little change
- Publication (2004) of guidelines recommending metabolic screening at baseline and at 3 months has had no discernable effect on screening practice

Morrato et al (Arch Gen Psychiatry 2010; 67:17-24).

Diabetes mellitus (DM)

- Prevalence
  - 3-4% of the world's population have DM
  - 70% of people with DM live in developing countries (more than 80% in 2030)
- Severe consequences
  - blindness, renal failure, amputation, cardiovascular disease, reduced life expectancy (≥ 10 years)
- Well-defined biological and behavioral risk factors
  - overweight and obesity (RR: 4.1-17.5)
  - physical inactivity (RR: 1.1-2.2)
  - other behavioral risk factors (e.g. diets low in whole grains and other sources of fibre, smoking)
- Combination of moderate weight loss, increased physical activity and dietary advice can lead to a 60% reduction in DM incidence

DM in SMI patients

- Prevalence of DM in SMI patients is higher compared with the general population
  - schizophrenia, bipolar disorder and schizoaffective disorder: 2-3 times higher
  - depression: 1.2-2.6 times higher
- Increase in ‘well-established’ DM risk factors probably accounts for much of the increased risk in these patients

DM and psychotropics

- Antipsychotics (AP)
  - diabetogenic risk 1.3 fold higher in people with schizophrenia taking atypical AP compared with those receiving conventional AP
  - risk DM-related adverse events differs between atypical AP (olanzapine, clozapine > risperidone, quetiapine > aripiprazole, ziprasidone)
- Antidepressants (AD)
  - specific data on the risk of DM associated with the use of AD are sparse, but increasing
  - concurrent use of tricyclic AD and SSRIs, long-term use for both tricyclic AD and SSRIs in at least moderate daily doses, as well as the use of AD medication in high-risk patients is associated with increased DM risk
- Mood stabilizers
  - valproate has elevated risk for the development of insulin resistance

Disparities in health care of DM in SMI patients

- Evidence that diabetes patients with mental health conditions are less likely to receive standard levels of diabetes care
  - no hemoglobin A(1c) testing: RR=1.24
  - no LDL-cholesterol testing: RR=1.25
  - no eye examination: RR=1.05
  - poor glycaemic control: RR=1.32
  - poor lipidemic control: RR=1.17
- Screening rates for metabolic abnormalities in people with SMI remain low, which may lead to prolonged periods of poor glycaemic control

Frayne et al (Arch Intern Med 2005; 165(22): 2631-2638).

Diabetic ketoacidosis (DKA)

- Potentially fatal condition related to metabolic stress, such as infection, trauma, myocardial infarction or stroke
- Symptoms include: increased thirst and urination, nausea and vomiting, abdominal pain, poor appetite, unintended weight loss, lethargy, confusion, coma
- Incidence of DKA nearly or more than 10-fold greater in those with schizophrenia compared to the general population
- Cases of DKA have been reported with all atypical antipsychotics, and with the conventional antipsychotic chlorpromazine
- Mortality of reported cases of DKA varies between 15.4% and 48%

Cohen and Correll (J Clin Psychiatry 2009; 70: 765-766); Henderson et al (J Clin Psychiatry 2007; 68: 533-541).

Cardiovascular diseases (CVD)

- Any disease that affects the cardiovascular system, with coronary heart disease (CHD) and cerebrovascular disease being the principal components

- Risk factors: smoking, obesity, hypertension, raised blood cholesterol, diabetes, unhealthy diet, physical inactivity and low socioeconomic status

- Prevalence accounts for 17.1 million or 29% of total worldwide deaths

- 82% of worldwide CVD deaths take place in developing countries due to global trade and food market globalization, increased obesity, physical inactivity and tobacco consumption, and less access to effective and equitable health care services

Economic development and summary prevalence of CVD risk factors in WHO subregions

	Poorest countries in Africa, America, South-East Asia, Middle East	Better-off countries in America, Europe, South-East Asia, Middle East, Western Pacific	Developed countries of Europe, North America, Western Pacific
Body Mass Index	**19.9-26.0**	**22.9-26.0**	**23.4-26.9**
Physical activity (% with no physical activity)	**11-23**	**15-24**	**17-20**
Low fruit and vegetable intake per day (grams)	**240-360**	**190-350**	**290-450**
Blood pressure (mean systolic pressure, mm Hg)	**125-133**	**124-133**	**127-138**
Mean cholesterol (mmol/l)	**4.8-5.1**	**4.6-5.8**	**5.1-6.0**

World Health Organization. World Health Report 2002: reducing risks, promoting healthy life. Geneva: World Health Organization, 2002.

CVD in SMI patients

- Patients with SMI are at significantly higher risk for cardiovascular morbidity and mortality than their counterparts in the general population
  - schizophrenia and bipolar disorder: up to 3-fold higher
  - depression: up to 5-fold higher
- Excess CVD is multifactorial and likely includes genetic and lifestyle factors as well as disease specific and treatment effects

Estimated prevalence and relative risk (RR) of modifiable CVD risks factors in schizophrenia and bipolar disorder compared to the general population

Modifiable risk factors	Schizophrenia		Bipolar Disorder	
	Prevalence	RR	Prevalence	RR
Obesity	**45-55%**	**1.5-2**	**21-49%**	**1-2**
Smoking	**50-80%**	**2-3**	**54-68%**	**2-3**
DM	**10-15%**	**2-3**	**8-17%**	**1.5-3**
Hypertension	**19-58%**	**2-3**	**35-61%**	**2-3**
Dyslipidemia	**25-69%**	**≤ 5**	**23-38%**	**≤ 3**
MetS	**37-63%**	**2-3**	**30-49%**	**1.5-2**

RR = relative risk

Correll (CNS Spectr 2007;12 (Suppl 17):12-20,35); De Hert et al (World Psychiatry 2009; 8: 15-22).

Coronary heart disease (CHD) in SMI patients

- Will become the leading cause of death in developing countries and emerge as the leading cause of death in the world during the 21st century
- Risk of CHD higher in SMI patients
  - schizophrenia: 2 to 3.6-fold increased risk
  - bipolar disorder: 2.1-fold increased risk
  - major affective disorder: 1.7 to 5-fold increased risk
- Depression increases risk of death or nonfatal cardiac events approximately 2.5-fold in patients with CHD

Cerebrovascular disease (CVD) in SMI patients

- Risk of CVD higher in SMI patients
  - schizophrenia: 1.5 to 2.9- fold increased risk
  - bipolar disorder: 2.1 to 3.3-fold increased risk
  - major affective disorder: 1.2 to 2.6-fold increased risk
- Obesity, diabetes, CVD as well as depressive symptoms are recognized as risk factors for CVD

CVD and psychotropics

- Antipsychotics (AP)
  - in addition to indirect, weight gain and obesity related mechanisms, there appears to be a direct effect of AP that contributes to the worsening of CVD risk
  - higher AP doses predict greater risk of mortality from CHD and CVD
- Antidepressants (AD)
  - SSRIs appear safe in cardiac populations, with few cardiac side effects
  - studies have found an increased risk of adverse cardiac events (10% increase heart rate, orthostatic hypotension, slow cardiac conduction, increased risk of arrhythmias) in patients using tricyclics
- Mood stabilizers
  - lithium generally can be safely used in cardiac patients

Sudden cardiac death (SCD) and psychotropics

- Patients with schizophrenia are three times as likely to experience SCD as individuals from the general population
- Dose-related increased risk of SCD found for both conventional and atypical antipsychotics
  - 1.31 vs. 1.59 (low dose, CPZ equivalents <100 mg)
  - 2.01 vs. 2.13 (moderate dose, CPZ equivalents 100-299 mg)
  - 2.42 vs. 2.86 (high dose, CPZ equivalents ≥300 mg)
- Dose-related increased risk of SCD found in current users of tricyclic antidepressants

Ray et al (N Engl J Med 2009; 360:225-235).

QTc-prolongation and psychotropics

- QTc values > 500 msec or increase of 60 msec compared with drug-free baseline put patients at significant risk of torsade de pointes (TdP), ventricular fibrillation and SCD
- Antipsychotics associated with a greater risk of QTc prolongation
  - pimozide, thioridazine, and mesoridazine
  - sertindole (?) and ziprasidone (?)
    - ZODIAC study (n = 18,154): no significant difference in risk of SCD between ziprasidone and olanzapine treated patients with schizophrenia
    - SCoP study (n=9,858): no significant differences between sertindole and risperidone recipients in cardiac events, including arrhythmias, requiring hospitalization
- Cases of TdP
  - reported with thioridazine, haloperidol, ziprasidone, olanzapine and tricyclic antidepressants
  - no cases of TdP have been reported with SSRIs
  - no cases of lithium-induced TdP

QTc-prolongation and psychotropics

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ORIGINAL ARTICLE

Prevalence and correlates of QTc prolongation in Italian psychiatric care: cross-sectional multicentre study

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Aims. In recent years several warnings have been issued by regulatory authorities on the risk of electrocardiogram abnormalities in individuals exposed to psychotropic drugs. As a consequence of these warnings, monitoring of the QT interval corrected for heart rate (QTc) has become increasingly common. This study was conducted to measure the frequency of QTc prolongation in unselected psychiatric patients, and to document the associated factors using a cross-sectional approach.

Method. The study was carried out in 35 Italian psychiatric services that are part of the STAR (*Servizi Territoriali Associati per la Ricerca*) Network, a research group established to produce scientific knowledge by collecting data under ordinary circumstances. During a three-month period, a consecutive unselected series of both in- and out-patients were enrolled if they performed an ECG during the recruitment period and were receiving psychotropic drugs on the day ECG was recorded.

Results. During the recruitment period a total of 2411 patients were included in the study. The prevalence of QTc prolongation ranged from 14.7% (men) and 18.6% (women) for the cut-off of 450 ms, to 1.26% (men) and 1.01% (women) for the cut-off of 500 ms. In the multivariate model conducted in the whole sample of patients exposed to psychotropic drugs, female sex, age, heart rate, alcohol and/or substance abuse, cardiovascular diseases and cardiovascular drug treatment, and drug overdose were significantly associated with QTc prolongation. In patients exposed to antipsychotic drugs, polypharmacy was positively associated with QTc prolongation, whereas use of aripiprazole decreased the risk. In patients exposed to antidepressant drugs, use of citalopram, citalopram dose and use of haloperidol in addition to antidepressant drugs, were all positively associated with QTc prolongation.

Conclusions. The confirmation of a link between antipsychotic polypharmacy and QTc prolongation supports the current guidelines that recommend avoiding the concurrent use of two or more antipsychotic drugs, and the confirmation of a link between citalopram and QTc prolongation supports the need for routine QTc monitoring. The relatively low proportion of patients with QTc prolongation not only suggests compliance with current safety warnings issued by regulatory authorities, but also casts some doubts on the clinical relevance of QTc prolongation related to some psychotropic drugs.

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QTc-prolongation and psychotropics

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First-generation antipsychotics and QTc: any role for mediating variables?

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Objective Corrected QT (QTc) interval prolongation is often associated with use of first-generation antipsychotics (FGAs). However, other factors require appropriate consideration, including age and gender, the role of other known medications associated with QTc prolongation, and severe comorbid conditions, such as co-occurring alcohol abuse/dependence. We aimed to study potential mediating roles of different, related, candidate variables on QTc.

Methods We capitalized on data from a large (N = 2366), cross-sectional, national survey, the STAR Network QTc study, using a representative sample of people taking FGAs, and recruited from mental health services across Italy.

Results About one-third of the sample was treated with FGAs, and almost one-tenth of the subjects took a different, additional, drug known to cause QTc prolongation. Our findings confirmed that there is an impact from FGAs, age, gender, alcohol misuse, and concurrent risky drugs on QTc. However, comorbid alcohol abuse/dependence and concurrent risky drugs did not mediate the effect of FGAs on QTc.

Conclusions Our findings showed that FGAs, concurrent risky drugs, and alcohol use disorders prolonged QTc. FGAs had a direct effect on QTc, confirming the need for clinicians to monitor a risk that could lead to sudden unexplained death.

QTc-prolongation and psychotropics

PLOS | ONE

RESEARCH ARTICLE

Antipsychotic Dose Mediates the Association between Polypharmacy and Corrected QT Interval

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Abstract

Antipsychotic (AP) drugs have the potential to cause prolongation of the QT interval corrected for heart rate (QTc). As this risk is dose-dependent, it may be associated with the number of AP drugs concurrently prescribed, which is known to be associated with increased cumulative equivalent AP dosage. This study analysed whether AP dose mediates the relationship between polypharmacy and QTc interval. We used data from a cross-sectional survey that investigated the prevalence of QTc lengthening among people with psychiatric illnesses in Italy. AP polypharmacy was tested for evidence of association with AP dose and QTc interval using the Baron and Kenny mediational model. A total of 725 patients were included in this analysis. Of these, 186 (26%) were treated with two or more AP drugs (AP polypharmacy). The mean cumulative AP dose was significantly higher in those receiving AP polypharmacy (prescribed daily dose/defined daily dose = 2.93, standard deviation 1.31) than monotherapy (prescribed daily dose/defined daily dose = 0.82, standard deviation 0.77) ($z = -12.62$, $p < 0.001$). Similarly, the mean QTc interval was significantly longer in those receiving AP polypharmacy (mean = 420.86 milliseconds, standard deviation 27.16) than monotherapy (mean = 413.42 milliseconds, standard deviation 31.54) ($z = -2.70$, $p = 0.006$). The Baron and Kenny mediational analysis showed that, after adjustment for confounding variables, AP dose mediates the association between polypharmacy and QTc interval. The present study found that AP polypharmacy is associated with QTc interval, and this effect is mediated by AP dose. Given the high prevalence of AP polypharmacy in real-world clinical practice, clinicians should consider not only the myriad risk factors for QTc prolongation in their patients, but also that adding a second AP drug may further increase risk as compared with monotherapy.

OPEN ACCESS

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Disparities in health care of CVD in SMI patients

- SMI patients have the least chance of receiving many specialized interventions or circulatory medications
  - people with schizophrenia are not adequately screened and treated for dyslipidemia (up to 88% untreated) and hypertension (up to 62% untreated)
  - significant deficit in the prescription of statins for schizophrenic patients
  - low rates of surgical interventions, such as stenting and coronary artery bypass grafting
- Lack of seeking medical care by SMI patients themselves, even during acute cardiovascular syndromes

Hepatitis in SMI patients

- Across different continents, persons with SMI have markedly elevated rates of hepatitis virus infection compared to the general population
- Overall, an estimated 20-25% of persons with SMI are infected with hepatitis C virus
- Most common transmission risks for persons with SMI are drug-use behaviors and sexual behaviors related to drug use
- Patients with mental illness are less likely to receive antiviral therapy

Respiratory diseases in SMI patients

- Tuberculosis
  - higher incidence among patients with schizophrenia compared with the general population
  - in some countries still occurs so frequently that mental hospitals have special wards for people with both tuberculosis and schizophrenia
- Pneumonia
  - schizophrenia is associated with a 1.4-fold greater risk of acute respiratory failure and a 1.3-fold greater risk of mechanical ventilation
- Chronic obstructive pulmonary disease
  - prevalence is significantly higher among those with SMI than comparison subjects
    - chronic bronchitis: schizophrenia (15%), bipolar disorder (25%)
    - asthma: schizophrenia (16%), bipolar disorder (19%)

Cancer risk in SMI patients

- Studies exploring relationship between SMI and all cancer types together have shown conflicting results
  - schizophrenic patients: decreased, higher or no different cancer risk compared to general population
  - bipolar disorder: no or slightly elevated risk
- Discrepancy of results possibly due to various confounding factors artificially lowering the rates of diagnosed and reported cancer in SMI populations
  - SMI patients are less likely to receive routine cancer screening
  - SMI patients have a shorter life expectancy and may die from cardiovascular reasons before reaching the expected age of death from cancer
  - protective effects of disease or antitumour properties of medication

Cancer risk and psychotropics

- Assumption has been made that exposure to prolactin-raising dopamine antagonists could result in breast cancer
  - current study database on antipsychotics and breast cancer risk is very limited
  - the majority of the few studies considering risk of breast cancer in patients treated with conventional antipsychotics did not uncover an increased risk of breast cancer.

Osteoporosis in SMI patients

- Schizophrenia: untreated patients have an increased risk of developing osteoporosis
  - due to the disease itself
  - due to risk factors related to their lifestyle (e.g. smoking, reduced physical activity, alcohol abuse, vitamin D and calcium deficiency, polydipsia)
- Depression: most studies have found low bone mineral density in patients with depressive symptoms or major depressive disorder
  - due to physiologic changes
  - due to the adoption of poor health behaviours

Osteoporosis and psychotropics

- Osteoporosis or low bone mineral density (BMD)
  - antipsychotics: clinical data are limited and contradictory. However, hyperprolactinemia with associated hypogonadism may be a risk factor
  - antidepressants: majority of studies report that the use of SSRIs is associated with low BMD
- Osteoporotic fractures
  - antipsychotics: conflicting results exist. Some studies report higher prevalence rates in patients with chronic schizophrenia, entirely or partly independent of the use of antipsychotics; other studies found significant increases (OR=1.2-2.6)
  - antidepressants: SSRIs are associated with high risk (OR= 1.5)
  - mood stabilizers: lithium is associated with lower fracture risk (OR= 0.6)

Sexual dysfunction in SMI patients

- Sexual dysfunction in SMI patients receives little attention from clinicians, having a significant negative impact on patients' satisfaction with treatment, adherence, quality of life and partner relationships
- Sexual dysfunction in SMI patients is, compared to normal controls, more frequent
  - schizophrenia: 30-80% of women and 45-80% of men
  - depression: up to 70%
- Patients with SMI are likely to engage in high-risk sexual behavior, putting them at risk of sexually transmitted diseases. However, sexual health education for these people tends to produce a reduction in sexual risk behavior

Sexual dysfunction and psychotropics

- Antipsychotics (AP)
  - relative impact of atypical AP on sexual dysfunction can be summarized as: risperidone > olanzapine ≥ ziprasidone > clozapine ≥ quetiapine > aripiprazole
  - conventional AP cause less sexual dysfunctions than risperidone but more than the other atypical AP
- Antidepressants (AD)
  - AD therapy (except for mirtazapine, nefazodone and bupropion) frequently induces or exacerbates sexual dysfunction, which occurs in approximately 50% of patients
  - Although sexual dysfunction has been reported with all classes of AD, SSRIs are associated with higher rates of sexual dysfunction (between 30% and 60%)

Stomatognathic diseases

- All studies without exception report poor dental health of people with SMI
- Poor dental health leads to functional difficulties in SMI patients (34% report that oral health problems make it difficult for them to eat)
- Factors influencing oral health include: type, severity, and stage of mental illness; lifestyle (e.g. smoking), effects of medication (dry mouth, carbohydrate craving); attitudes and knowledge of dental health teams concerning mental health problems
- Antipsychotics, antidepressants and mood stabilizers all cause xerostomia, leading to caries, gingivitis and periodontal disease
- Oral health is a frequently disregarded health issue among SMI patients. Studies report low rates of dental examination within the past 12 months (43% -77%)

Treatment

- Rates of undiagnosed and untreated medical illnesses are higher in individuals with severe mental illness (SMI), compared to the general population
- Disparities in health care access, utilization and provision, contribute to these poor physical health outcomes
- Confluence of patient, provider, treatment and system factors has created a situation in which access to and quality of health care is problematic for individuals with SMI
- Many psychiatrists consider their primary or, even, sole function to provide clinical care in terms of psychiatric symptom control and are reluctant to monitor physical health

Barriers to recognition and management of physical illness in patients with SMI

Patient and illness-related factors
Difficulty comprehending health care advice and/or carrying out required changes in lifestyle due to psychiatric symptoms (e.g. cognitive deficits, negative symptoms, poor insight, suspicion)
Difficulty comprehending health care advice and/or carrying out required changes in lifestyle due to adverse consequences related to mental illness (e.g. low educational attainment, reduced social networks, lack of employment and family support, poverty, poor housing)
Severity of mental illness (SMI patients have fewer medical visits, with the most severely ill patients making the fewest visits)
Less compliant with treatment
Unawareness of physical problems due to cognitive deficits or to a reduced pain sensitivity associated with psychotropic medication
Migrant status and/or cultural and ethnic diversity
Lack of social skills and difficulties communicating physical needs

Barriers to recognition and management of somatic illness in patients with SMI

Clinician-related factors
Psychiatrist-related
Tendency to focus on mental rather than physical health (“our primary function is the management of mental health symptoms”) with infrequent baseline and subsequent physical examination of patients **Poor communication with primary care health workers** **Physical complaints regarded as psychosomatic symptoms** **Suboptimal and worse quality of care offered by clinicians to patients with SMI.** Lack of assessment, monitoring and continuity of care of the physical health status of people with SMI **Guidelines perceived as a threat to autonomy, not well known or clinically not accepted** **Lack of knowledge regarding medical issues by the psychiatrist** **Erroneous beliefs** (SMI patients are not able to adopt healthy lifestyles, weight gain is mainly adverse effect of medications, lower cardiac risk medications are less effective)
Primary care physician-related
Stigmatization of people with mental disorders **Physical complaints regarded as psychosomatic symptoms** **Suboptimal and worse quality of care offered by clinicians to patients with SMI.** Lack of assessment, monitoring and continuity of care of the physical health status of people with SMI
Other
Complexity and time intensity of coordinating both medical and psychiatric care/medications

Barriers to recognition and management of somatic illness in patients with SMI

Service-related factors
Financial barriers, especially in developing countries; paucity of funding in some countries of general somatic care for patients with SMI
High cost of (integrated) care
Lack of access to health care
Lack of clarity and consensus about who should be responsible for detecting and managing physical problems in patients with SMI
Fragmentation or separation of the medical and mental health systems of care, lack of integrated services
Under-resourcing of mental health care that provides little opportunity for specialists to focus on issues outside their core specialty

Monitoring guidelines - Physical health checks

- weight gain and obesity
  - Body Mass Index (BMI)
  - Waist Circumference (WC)
- dietary intake
- activity level and exercise
- use of tobacco and alcohol or other substances
- blood pressure
- fasting glucose and lipid levels (esp. TG and HDL-cholesterol)
- cardiovascular disease risk and ECG parameters
- prolactin levels (if symptomatic)
- dental check
- liver function tests, blood count, thyroid hormone, electrolytes (periodically, as indicated)

Monitoring guidelines - Weight gain and obesity

- **Monitor and chart BMI and WC of *every* SMI patient at *every* visit, regardless of the medication prescribed**
- **Encourage patients to monitor and chart their own weight**
- **BMI and WC assessment is simple, inexpensive and can easily been done with a weighing scale and waist tape measure**

Monitoring guidelines - Waist circumference (WC)

- More useful measurement than BMI
  - stronger indicator for systolic blood pressure, HDL-cholesterol, triglycerides, and future type 2 diabetes, cardiovascular disease and metabolic syndrome
- Simple tool to assess the likelihood of insulin resistance
  - WC < 100 cm excludes insulin resistance in 98% of males and 94% of females
- Sex-and race-specific criteria in defining elevated WC are available

Monitoring guidelines - Blood pressure (BP)

- **Assess BP *routinely, even at every visit***
- **High BP in SMI patients is often missed**
  - **Hypertension**
    - **systolic BP ≥130 mm Hg**
    - **diastolic BP ≥ 85 mm Hg**
  - **Prehypertension**
    - **systolic BP 120 to < 130 mm Hg**
    - **diastolic BP 80 to < 85 mm Hg**
    - **requires lifestyle modifications to prevent heart disease**
- **Cost for measuring BP is low**

Monitoring guidelines - Fasting plasma glucose (FPG)

- Collect baseline measure of plasma glucose level for *all patients before starting treatment*
- Carry out tests at 6 and 12 weeks to capture early cases of hyperglycemia, and then, at minimum, yearly
- Conduct blood glucose measurement in fasting patients (= most sensitive measurement). If problematic, conduct a random blood glucose test (and/or haemoglobin A1C test)
- Patients with significant risk factors for diabetes
  - should be monitored at baseline, 6 and 12 weeks after starting medication and then approximately every 3-6 months
- Patients who are gaining weight (≥ 7%)
  - should be monitored every 4 months
- Diabetes
  - FPG ≥ 126 mg/dl or haemoglobin A1C value ≥ 6.5%
    - consultation with an internist or other primary health care provider for further assessment
  - FPG between 100 and 125 mg/dl or haemoglobin A1C values of 5.7-6.4% (prediabetes)
    - also prompt closer assessment and follow-up

Monitoring guidelines - Fasting lipid levels

- Assess fasting lipid parameters (especially triglycerides and HDL-cholesterol) at baseline and at 3 months, with 12-monthly assessments thereafter
- Abnormal fasting lipid levels:
  - total cholesterol
    - without diabetes: > 5 mmol/l (190 mg/dl)
    - with diabetes: > 4.5 mmol/l (175 mg/dl)
  - LDL-cholesterol
    - without diabetes: > 3 mmol/l (115 mg/dl)
    - with diabetes: > 2.5 mmol/l (100 mg/dl)
- Cost and lack of availability of this assessment may not make it feasible as a routine measure in all settings and patients

Monitoring guidelines - Cardiovascular disease (CVD) risk

- **Ask patients about heart risks:**
  - **family history of early sudden cardiac death (<50 in males, <55 in females)**
  - **previous prescription of cardiac medications or anti-hypertensives**
  - **history of murmur**
  - **irregular heart beat or tachycardia at rest**
  - **episode of simple syncope in the past**
- **Although often difficult to obtain in the psychiatric setting, measurement of ECG parameters as a baseline requirement deserves serious consideration to comprehensively assess cardiac health**
- **As a general rule, *every* patient must have a *one-single* ECG measurement prior to the initiation of medication. Hereafter, depending on the advice given by a cardiologist, ECG monitoring can be repeated**
- **Calculate the patient's individual CVD risk from the patient's age, sex, presence or absence of diabetes, smoking habit, systolic BP, total cholesterol or the ratio of total cholesterol to HDL-cholesterol**

Monitoring guidelines - Prolactin (PRL) measurement

- Measure PRL only if sexual or reproductive system abnormalities are reported (these need to be asked about directly and monitored)
  - reproductive system abnormalities
    - amenorrhea or oligomenorrhea (i.e, <9 periods per year), galactorrhea, gynecomastia in males, and/or breast tenderness and pain in females
  - sexual dysfunction
    - new symptoms and/or those that coincided with antipsychotic treatment or dose change, including decreased libido, erectile or ejaculatory dysfunction, problems with arousal or orgasm
- Normal PRL values in most laboratories
  - men: 20 ng/ml (424 mIU/mL)
  - women: 25 ng/ml (530 mIU/L)

How and when to screen

- During initial phases of treatment, it is specifically important to measure weight weekly/at each visit to identify patients who gain weight rapidly
- If the patient has abdominal obesity, hypertension, prediabetes, diabetes, or dyslipidemia, he/she should be referred to a primary care provider to treat these conditions, unless simple healthy lifestyle guidance or behavioral adjustment and/or switching to a lower cardiometabolic risk medication can address these medical conditions adequately
- Use an algorithm, monitoring form or risk chart to screen patients (simpler option than the more complex and detailed guidelines)
- Record physical health assessments on charts showing the times and results of the assessments compared with reference ranges

Routine measurements for use in monitoring and evaluation of physical health in SMI patients with normal baseline values

	Baseline	6 weeks	3 months	At least at 12 months and annually thereafter
Personal and family history	X			
Smoking, exercise, dietary habits	X	X	X	X
Weight	X	X	X	X
Waist circumference	X	X	X	X
Blood pressure	X	X	X	X
Fasting plasma glucose	X	X[1]	X	X
Fasting lipid profile	X	X[1]	X	X
ECG parameters	X			
Prolactin	X[2]		X[3]	X[3]
Dental health	X			X

1 This early blood sugar and lipids assessment has been recommended in Europe, but not in the US
2 If possible to have some reference values, or, if this is too expensive, only in case sexual or reproductive system abnormalities are reported
3 Only in case of sexual dysfunction that coincided with antipsychotic treatment or dose change

Impact of health actions on one´s overall health

Health act	Impact on one´s overall health
Maintenance of ideal body weight Weight loss 4-5% 5-7% 6-7% 10%	35-60% ↓ CHD Eliminate the need for anti-hypertensive medications in adults and elderly 58% reduced risk for type 2 DM in adults Improvement of the MetS by decreasing LDL-cholesterol and fasting insulin Reduction lifetime risk for heart disease up to 4% and increase life expectancy for up to 7 months
10% ↓ blood cholesterol	30%↓ CHD
4-6 mmHg ↓ high BP (>140/90 mmHg)	16%↓ in CHD and 42%↓ in CVD
Stop smoking	50-70% ↓ in CHD
Maintenance of active lifestyle (+/- 30 min walk daily)	35-55% ↓ in CHD (women) 18% ↓ in CDH (men) 27% reduction in CVD 40-50% ↓ in risk of cancer 33-50% ↓ in risk of developing DM

CHD – coronary heart disease; DM – diabetes mellitus; MetS – metabolic syndrome; BP – blood pressure; CVA – cerebrovascular accident

Treatment guidelines - Diet

- Interventions that address nutrition and weight management should become a routine part of psychiatric care
  - many SMI patients do not know the components of a healthy diet
  - patients should be advised to avoid high calories, high fat, and nutritionally poor food (e.g. fast food and unhealthy snacks), and to consume healthy alternatives (e.g. fresh fruit and vegetables, fish, and lean meats in a balanced way)
  - lifestyle changes should be gradual
- Various educational and psychosocial programs that address the issues of health and wellness exist. These programs have been shown to be effective in people with SMI

Examples of behavioral interventions to improve the health of patients with SMI

Area of concern	Educational suggested tools
Diet	**Healthy eating behavior** -Cutting down on fast food -Increase healthy food items (fruits, vegetables, fish), decrease high glycemic index food items and monounsaturated fats -Decrease processed fat free food -Making healty snack choices -Controlling portion size -Consume 4-6, but small meals -Eating more slowly -Minimizing intake of soft drinks with sugar and with artificial sweetener **Educational** -Reading food labels -Learning to discern differences between physiological and psychological appetite and eating -Keeping food diaries/plans/exchange tables -Learning cooking skills -Healthy food shopping
Exercise	**Physical activity** -Keeping activity diaries, daily activity list -Increasing physical activity such as moderate intensity walking -Reduce sedentary behaviors (TV watching, video/computer games, etc) -Treating/reducing sedation and extrapyramidal effects of medications

Adapted from Vreeland B (J Clin Psychiatry 2007; 68(Suppl. 4):8-13).

Treatment guidelines - Physical activity

- Effects of physical activity
  - 150 to 250 min a week: modest weight loss and effective in preventing weight gain
  - >250 min a week: clinically significant weight loss
- People with schizophrenia are significantly more sedentary than the general population
  - only 25.7% meet the minimum public health recommendation of 150 min a week of at least moderate-intensity physical activity
- Advise patients to engage in at least 30 minutes of moderately vigorous activity (at least a brisk walk) on most days of the week
- In patients who are obese, physical exercise should be accompanied by proper diet to achieve significant weight loss

Treatment guidelines - Smoking

- Up to 85% of individuals with SMI will die and/or have a reduced quality of life because of a tobacco-related disease
- Treating tobacco dependence is effective in patients with SMI and does not worsen mental state
- Advice and encourage SMI patients strongly to stop smoking (cessation associated with approximately a 50% ↓ in CHD risk)
- Assist patients in developing a quit plan, and arrange follow-up. If necessary and possible, patients should be referred to a smoking cessation service
- Abrupt cessation has potentially negative consequences
  - serious risk of toxicity with clozapine and olanzapine. Plasma clozapine levels must be monitored closely and adjustments made in dosage, if necessary, for at least six months after cessation
  - short-term increased risk for diabetes. Withdrawal of nicotine may lead to increased appetite and excess caloric intake (provide dietary advice and/or nicotine replacement)

Treatment guidelines - Blood pressure (BP)

- Target BP levels of less than 130/85 mmHg are recommended
- Lifestyle changes, such as stopping smoking, reducing salt intake, weight reduction and increased exercise, may be sufficient to reduce mildly elevated BP, although some patients are likely to require pharmacological therapy
- Recently updated European guidelines stress the importance of choosing anti-hypertensive agents best suited to the individual patient’s needs

Treatment guidelines - Oral health

- Oral health is as important as weight for routine monitoring
- Assess risk factors for a poor oral health (e.g. smoking, medication side effects) and individual oral care needs
- Advice on the dietary control of sugars and the importance of sugar free lubrication to reduce the adverse oral side effects of psychotropic medication causing xerostomia (dry mounth)

Treatment guidelines - QTc prolongation and sudden cardiac death (SCD)

- Antipsychotics or antidepressants known to be associated with QTc prolongation should not be prescribed for SMI patients with
  - known heart disease
  - a personal history of syncope
  - a family history of SCD at an early age (< 50 years in males and < 55 in females, especially if both parents had SCD), or congenital long QT syndrome
- Withdrawal of any offending drugs and correction of electrolyte abnormalities are recommended in patients presenting with torsade de pointes

Specific treatment advice on medication

- Give consideration to switching antipsychotic, antidepressant and/or mood stabilizer medication when a SMI patient
  - gains significant amount of weight (>5% of initial weight)
  - shows hyperglycemia, hyperlipidemia, or other significant adverse effects (e.g. clinically significant cardiac side effects)
- The switching protocol should consider the entire psychiatric and physical condition of the patient and the pharmacological profiles of both agents
- Another option is to add a pharmacological agent to reverse or prevent the medication-induced adverse event (e.g. metformin or topiramate to attenuate weight gain in patients taking antipsychotics)
- Refer the SMI patient to specialist services, including diabetology, endocrinology and cardiology, if diabetes or another severe physical illness has been diagnosed

Recommended system and individual level actions to address gaps in the assessment and treatment of physical health problems in SMI patients

System level actions
Designate the population with SMI as a health disparity population
Educate the health care community
Train the health care community
Improve access to and care of physical health of the SMI population
Reduce stigma and discrimination
Bridge the collaboration gap between physical and mental health care and promote a policy of coordinated and integrated mental and physical health care for persons with SMI
Address funding for these necessary service improvements

Recommended system and individual level actions to address gaps in the assessment and treatment of physical health problems in SMI patients

Individual level actions
Take responsibility for the physical health of the SMI patient
Screen the patient's personal and family history at baseline to identify high-risk patients and to ensure early detection of changes in critical parameters
Adopt ongoing surveillance methods
Use an algorithm, monitoring form, or risk chart during the patient's screening
If weight gain (>5% of initial weight), glucose abnormalities, hyperlipidemia, or other adverse effects during therapy occur, consider switching to medications with lower risk profiles
Communicate monitoring findings to the primary care teams and specialist services, including diabetology, endocrinology and cardiology
Forge stronger collaborations with these medical specialists and other health care professionals
Include lifestyle modifications into education and treatment programs for SMI patients, incorporating nutrition, exercise and behavioural strategies
Strive to encourage and improve the patient's adherence to both psychiatric/medical and behavioural interventions
Support wellness, personal empowerment and individual responsibility to enable healthy choices for recovery, and promote individual efforts

Recommended system level actions to address gaps in the assessment and treatment of physical health problems in SMI patients

- **Designate the population with SMI as a health disparity population**
  - psychiatrists can play an important role in this process of raised awareness by addressing the current disparity with policy makers and budget holders
- **Educate and train the health care community**
  - national and local education initiatives should be implemented to disseminate information widely about physical health risks in persons with SMI and to encourage awareness of the current disparity
  - mental health care personnel need to be trained in adequately assessing and measuring CVD health and other (e.g. oral health) risks. Training in SMI should be offered to primary care clinicians

Recommended system level actions to address gaps in the assessment and treatment of physical health problems in SMI patients

- **Improve access to and care of physical health of the SMI population**
  - state and health care institutions have to build adequate capacity to ensure prevention, screening, and treatment of general health care issues of the SMI population
- **Reduce stigma and discrimination**
  - education interventions and personal social contact with persons with SMI can be used to reduce public stigma and discrimination. If necessary, anti-discrimination legislation should be enforced to ensure equal access to health care

Recommended individual level actions to address gaps in the assessment and treatment of physical health problems in SMI patients

- **Take responsibility for the physical health of the SMI patient**
  - **unless there is a clear provision of specific general somatic health care services for SMI patients, the psychiatrist should assume responsibility for the somatic health of his/her patients. He/she has to keep a check on the situation, as SMI patients may not seek help themselves until the problem is severe, or may not be aware of potentially harmful physical conditions until monitoring has been done**
- **Screen the patient's personal and family history at baseline to identify high-risk patients and to ensure early detection of changes in critical parameters**
  - **for patients with a personal or family history of obesity, high blood pressure, diabetes, heart disease or CVA, or with high or borderline values on metabolic criteria, drugs with lower risk of adverse effects should be chosen**

Recommended individual level actions to address gaps in the assessment and treatment of physical health problems in SMI patients

- Communicate monitoring findings to the primary care teams and specialist services, including diabetology, endocrinology and cardiology
  - ensure that people with SMI who have been identified to be at risk of developing CVD and/or diabetes be managed. People with SMI who have established CVD and/or diabetes should be treated in primary care
- Force stronger collaborations with these medical specialists and other health care professionals
  - integrated care models should be developed, including:
    - co-location of services (locating a primary health care team close to mental health services with good links between primary care and mental health staff)
    - having staff from one service visit another on a regular basis
    - appointing case managers to liaise between services and coordinate the overall care for the patient
    - a multidisciplinary team of health workers including physicians as well as psychiatrists

Recommended individual level actions to address gaps in the assessment and treatment of physical health problems in SMI patients

- Strive to encourage and improve the patient's adherence to both psychiatric/medical and behavioral interventions
- Support wellness, personal empowerment and individual responsibility in patients with SMI, enabling them to make healthy choices for recovery, and promote their individual efforts
  - specific programs (e.g. the Health and Recovery Peer Program) exist to help people with SMI to become more effective managers of their chronic illnesses, improving a range of self-management and health outcome measures, including patient activation and greater likelihood of using primary care medical services

Grazie per l’attenzione…

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