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Recommendations for Mental Health Departments regarding activities and measures of contrast and containment of the SARS-COV-19 virus

PACINI EDITORE MEDICINA

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RECOMMENDATIONS FOR MENTAL HEALTH DEPARTMENTS REGARDING ACTIVITIES AND MEASURES OF CONTRAST AND CONTAINMENT OF THE SARS-COV-19 VIRUS

COMMUNITY MENTAL HEALTH CENTRES. GENERAL OPERATING INDICATIONS

1. All visits which are not of an urgent or emergency nature (including individual psychotherapy/ group therapy and/or rehabilitation activities and team meetings) must be suspended until the state of emergency is off.

2. Planned injections of long-acting antipsychotic drugs must be considered equivalent to emergencies as their postponement would put patients' mental health at risk. At present, therefore, they must be carried out with due regularity.

3. The scheduled outpatient activities of the CMHC are re-evaluated according to individual cases trough telephone contact by the staff members who have in charge the user, in order to check his/her physical health (any symptoms of cough, fever ≥ 37.5 °, sore throat, respiratory fatigue) and mental health (change of psychic status respect to the most recent evaluation, including concerns about the current situation) together with the health conditions of family members.

4. During the telephone interview, informations should be provided about the overall functioning of services; general recommendations regarding the necessity of limiting social contacts should be reminded; moreover, the opportunity to maintain or reschedule the next visit should be jointly assessed. In all cases, the possibility of unscheduled direct access in case of necessity or emergency should be reminded, along with the usual opening hours of the CMHC, which should remain unchanged compatibly with the staff resources available.

5. The reference psychiatrists must maintain regular phone contacts with those patients who are clinically stable. On site visit should be granted for those who are not clinically stable. All the aforementioned

activities (included phone contacts) must be reported in the medical records and in the national information system platform (service code: interview).

6. Home visits should be carried out by the least possible number of staff members, just those who are necessary for safety reasons; in these cases staff will use always only service cars. Home visit should be preceded by a phone contact with the user or with his/her caregivers, in order to evaluate the physical health status of the patient and of family members and assess the risk of exposure for staff members. Operators will wear Personal Protective Equipment (PPE), taking all precautions regarding personal distance. Whenever possible, home visits should be carried outside, in open spaces.

7. If recipes are needed, they will be written as dematerialized through the appropriate national platform; they will be written in paper form only when the dematerialized way is not available; in these cases recipe should be delivered in a sealed envelope**.**

PREVENTION MEASURES

All operators must be aware of the following key general informations and behavioural indications:

1. According to currently available data, symptomatic people are the most frequent cause of the virus spreading. WHO considers new coronavirus infection as infrequent before symptoms develop. A preliminary (if possible, telephone) history aimed at identifying the symptoms of COVID-19 infection is therefore of crucial importance. Onset symptoms: the most common are fever above 37.5 ° C in 86% of cases; dyspnea (difficulty breathing) in 82%; cough in 50%; the least common are gastrointestinal symptoms (diarrhea) and hemoptysis (blood flow from the respiratory tract, for example with a cough), in 5% of cases.

2. Recommendations in case of symptoms or suspected cases are : a) people who are symptomatic (fever and/ or other symptoms) should be invited to stay at home, avoiding to go to the emergency rooms or to the doctors' offices; b) they should call by phone their GP (or Pediatrician) or Community Medical Guard (nights; holidays); c) people who in addition to fever and other sympoms suffer from dyspnoea and /or cough and / or diarrhea and /or hemoptysis should be invited to call immediately the number 118.

3. It is imperative avoiding touching eyes, nose and mouth with hands. The virus can penetrate the body if it comes into direct contact with the mucous membranes of the nose, mouth and eyes.

4. Hand washing eliminates the virus and prevents infection. Indeed, risk does not derive from contact with objects, but from the possible contamination of the hands which then come into contact with the mucous membranes. Therefore it is absolutely necessary to wash hands thoroughly with soap and water for at least 30 seconds (or, alternatively, with 60% alcohol-based gel), in particular after touching objects that may have been touched by other people as well as by same owners/users of the items before washing their hands.

5. Operators are particularly recommended to carefully disinfect objects to which little attention is usually paid: mice, monitors and computer keyboards, their power buttons, landlines and smartphones, glasses, armrests of chairs and armchairs, drawer handles.

6. The toilets - both for operators and for patients - must always be equipped with the necessary material for washing hands (soap, hydroalcoholic gels/disinfectants, paper towels) and must be carefully cleaned by

the cleaning staff . The conditions of use of the toilets must be monitored by the staff members of Mental Health Department's, generally by the Head Nurse.

7. Patients' stay in waiting rooms should be limited as much as possible, by carefully arranging/ rearranging appointments. Newspapers and magazines and all paper materials in general must be carefully removed from the waiting rooms. In waiting rooms, a minimum distance of two meters must be provided between the chairs. Moreover, in the waiting rooms, in the infirmaries, in the places where acceptance is carried out and in medical studies, the poster of the Ministry of Health must be displayed bearing the behavioral indications suitable to counter the spread of COVID-19.

8. At the entrance of the CMHCs, users will receive the instructions to clean their hands with antiseptic gel and will be directed with appropriate signs to the Filter Zone of the acceptance or other dedicated place that allows the maintenance of the prescribed distances. Access to the facilities is allowed only to people who needs care and to one relative or carer, only when deemed strictly necessary**.**

PROCEDURES FOR THE EXECUTION OF MANDATORY MENTAL HEALTH TREATMENTS (TRATTAMENTI SANITARI OBBLIGATORI, TSO) AND MANDATORY MENTAL HEALTH EVALUATIONS (ASO, ACCERTAMENTI SANITARI OBBLIGATOR)

Considering that TSO/ASO procedures involve conditions quite similar to those faced by emergency workers (118), where people often unknown are assisted, staff operates in an unprotected environment (street, patients' home etc.) and is involved in situations where direct contact with an agitated or behaviourally disorganized person is possible, the following general procedures are recommended:

• staff should be equipped with the maximum permitted level of PPE;

• the maximum possible safety distance should be kept;

- only one staff member, generally the psychiatrist, should approach the client for the interview, which must however take place at a minimum safety distance of 1 meter, or higher whenever possible;

• If the intervention occurs in a restricted environment (i.e. at home) , the interview should possibly carried out in a ventilated room, with open windows or in a space outside the home, whenever possible;

• in case of lack of a sufficient number of second/third level PPE, the FP2/FP3 mask, protective goggles, gloves and disposable gowns will necessarily be worn by those who carry out the interview and health procedures, (i.e. injections, see next paragraph) or who will accompany the patient to the hospital in ambulance.

RECOMMENDATIONS REGARDING HEALTH PROCEDURES AND ADMINISTRATION OF ORAL/IM DRUGS

• The administration of "depot" drugs, both at home and on site, should be eventually postponed if the client clearly manifests signs and symptoms of a respiratory syndrome, and rescheduled the following week as regards "depot" drugs, except when the administration cannot be postponed due to clinical reasons . As regards the suggested procedures for the administration of the drugs, see the following paragraphs.

• In the case of daily administration of oral medications, at home or on site, it is recommended to wash hands beforehand and then disinfect them with hydroalcoholic solution, then proceeding to pack a small gauze container in which to store drugs to be administered; the container has to be placed on a cleaned table, asking the client to take the drugs directly from it and assume pills in your presence (if direct intake

control is indicated). During the operation, wear the surgical mask, gloves and an ordinary gown if the client shows no sign or symptoms of a respiratory syndrome and there is no fever; however, in order to limit contact with the patient, a safety distance of at least one meter must be kept, possibly even greater if space permits; if the patient shows respiratory symptoms, it is advisable the use of second/third level PPE, (FP2/FP3 mask, protective goggles, gloves and disposable gowns); in case these PPE should'nt be available, as an alternative use surgical masks, ordinary glasses / sunglasses, disposable gloves, ordinary overalls, which should be removed immediately after use and sent for washing. After administration, wash and disinfect the hands again.

RECOMMENDATIONS REGARDING SEMI-RESIDENTIAL ACTIVITIES (DAY CENTER, COMMUNITY DAY-HOSPITAL)

Since these are activities that normally involve the presence of more than one person, they will be suspended whenever possible according to the functional characteristics of the Day Center / Day Hospital and the clinical needs of the users' groups; as an alterative, a reduction in access must be expected, however applying the general and specific prevention rules already described. In case of suspension of activities, an alternative program will be jointly defined with each user (individual interviews scheduled at the CMHC or by telephone/ video call). The capacity of these services as well as of CHMCs to maintain regular telephone/ video call contacts with clients should be granted, on particular as regard the accessibility of phone lines and the availability of apps for video-call.

RECOMMENDATIONS REGARDING RESIDENTIAL FACILITIES

Residential activities should continue respecting the following requirements:

1. New accesses should be limit to non-postponable cases (eg: as an alternative to hospitalization or in case of post-acute phase after hospitalization).

2. In case of new accesses, the state of physical health on the client (any symptoms of cough, fever ≥ 37.5, sore throat, respiratory fatigue) should be checked, evaluating the presence of any contacts at risk in the previous 14 days.

3. In the case of respiratory symptoms and/or previous contacts at risk and if the admission cannot be postponed, the client could be admitted only if the facility has isolation spaces (single room with autonomous toilets) and the equipment of PPE for the staff; moreover the rapid execution of a pharyngeal swab should be granted. Otherwise, home care should be planned for the client or his/her admission to another dedicated place where isolation and safety conditions may be guaranteed (i.e sheltered apartments specifically devoted/converted for this emergency).

4. Information regarding safety and preventive rules should be granted for users, both individually and through printed material, actively promoting frequent hand washing and social distancing; daily checks of body temperature and of eventual respiratory symptoms should be carefully executed.

5. The access of visitors should be limited to situations deemed strictly indispensable by the manager of the structure, favoring telephone contacts. The authorized visitor will wear the surgical mask, will provide to clean his hands and to keep the distance of at least 1 meter or more. Meetings in outdoor spaces will be favored.

6. Exit permits should be restricted to situations deemed strictly indispensable by the manager of the facility, taking into account the clinical conditions of the user.

RECOMMENDATIONS REGARDING INPATIENT UNITS

MANAGEMENT OF INPATIENTS

1. Check the temperature of the patients twice a day, to monitor the sudden onset of the following symptoms of acute respiratory infection: fever> 37.5 ° C, cough or breathing difficulty.

2. For asymptomatic patients, apply the general Covid infection risk prevention and mitigation measures.

3. In the presence of one of the above signs and symptoms, implement the following measures, as per circular DS n.26086 of 10.3.2020:

• the symptomatic patient must wear a surgical mask;

• if his collaboration in wearing it is not possible, he must be isolated from the other patients in a single room and must not be allowed to access the common areas;

• all operators who come into contact with him must use protective PPE as for TSO.

With all collaborative patients granting the possibility of maintaining the safety distance in the execution of a normal maneuver / procedure (e.g. execution of blood samples, voluntary IM therapies, etc.):

• use surgical masks, disposable gowns / disposable aprons, gloves, protective goggles / visor;

With uncooperative patients (agitated, violent, hostile, oppositional, etc.) and the impossibility of maintaining the safety distance:

• use FFP2 /FFP 3 masks, disposable gowns / disposable aprons, gloves, protective goggles / visor, overshoes;

• contact an infectious disease specialist for further diagnostic and therapeutic indications including eventual indication to the swab;

- keep the patient isolated from other patients until the outcome of the swab is available, if indicated. If the patient is asymptomatic but his/her physical condition is doubtful, a two weeks surveillance in isolation should be adopted;

• stop any transfer to post-hospital facilities and dimission until sufficient collaboration is reached, and the patients has been asymptomatic for two weeks or with negative swab**.**

MANAGEMENT OF CASES TO BE ADMITTED

- Carry out the pre-triage in the dedicated area of the Emergency Dept of the Hospital.
- In case the patient does not require urgent hospitalization, he will be sent back to his home with the advice to contact his/her GP and/or the reference CMHC. If the patient is already in charge of the CMHC or the clinical situation requires it, it is the responsibility of the consultant psychiatrist who visited the patient at the Emergency Dept. of the Hospital to contact the reference CMHC for the appropriate report of the case.
- If the patient has to be hospistalized and is able to collaborate in keeping a distance with others greater than 1 meter, he will be admitted only if he/she resulted negative at the pre-triage evaluation.
- In case the patient is resulted positive at the pre-triage and needs hospitalization, he will be admitted and kept isolated from the other patients for two weeks, if he is unable to collaborate in wearing the surgical mask and keep the distance with others greater than 1 meter; this measure should applied in case the swab was deemed not indicated or until the outcome of the swab has been known.
- When the patient needs urgent voluntary hospitalization or compulsory admission and the pre-triage was made impossible due to the critical conditions of the patient (e.g. uncooperativeness, agitation, violent and hostile behaviour etc.) he/she will be directly sent to the triage at the Emergency Dept. as any other patient in red code. See below for further recommendations.
- In the event that the patient who arrives in the emergency room for an acute psychiatric disorder results positive to COVID-19, he must be hospitalized in the COVID area (infectious diseases, internal medicine, intensive care etc) like all the other COVID + patients. In these cases, the therapeutic aspects concerning mental disorder are managed by a consultant psychiatrist who will be equipped with all the Personal Protection Devices which are necessary.

- If a COVID + psychiatric patient who absolutely needs to be hospitalized in the psychiatric unit in light of an acute psychiatric condition making the case not manageable in the Covid Unit, the indications to follow are:

  • Isolate the Covid + patient in a single room (if necessary, seclusion or restraint) equipped with a separation door, a buffer zone, a separate bath and oxygen. You must first agree with the health management of the hospital to have all the structural supplies and PPE necessary to treat a Covid patient.

  • the infected patient should use the surgical mask. Only a few operators should have access to the patient, wearing the PF2-3 masks and all the other Personal Protective Devices. In case the physical conditions become extremely severe, the patient must be transferred to the Covid ward. In these cases, appropriate pharmacological treatment should be provided, including the use of drugs for the control of agitation, paying attention to the use of benzodiazepines, which alter the respiratory function, in particular long-life benzodiazepines (eg, clordemetildiazepam), even in patients without dyspnea , because they could develop it quickly.

  • Basing on the initial experience of the Codogno Hospital Psychiatric Ward, it is strongly recommended whenever possible separating one area of the ward from the remaining, delimiting a buffer zone for the dressing of the operators who entered the area where positive patients with mild symptoms and patients waiting for outcome of the swab are hospitalized.

  - However, basing upon the overall experience of the Region Lombardy, it is strongly recommended that all positive patients are treated in the Covid units of the Hospital, where psychiatrists will carry out consultancy activities.
  - In some situations a separated room or area of the psychiatric unit could be equipped for positive patients or better, an entire psychiatric ward specifically equipped could be devoted for caring psychiatric patients who are Covid+ on a Regional basis.
  - Whichever of these solutions is realized, when the respiratory syndrome due to Covid infection becomes prevalent and very intensive care (intubation) is needed, the patient must transferred to the Covid unit.

RECOMENDATIONS REGARDING THE STAFF

Basing on Government decreed, employers are advised to facilitate the use of ordinary holiday periods and other contractual exemptions from the service, compatibly with the guarantee of essential services.

Without prejudice to the legislative provisions (suspension of any leave of absence as regard to technical health personnel, as well as personnel whose activities are necessary to manage the activities required by the Crisis Units set up at regional level), it is however suggested to facilitate the use of ordinary leave, in particular unused holidays and working hours in excess to be recovered, in case of a drop in the clinical activity for urgent patients taking place due to emergency. These measures are finalized to avoid an excessive crowding in the health facilities, and also to preserve part of the resources in the perspective of need of a turnover.

RECOMMENDATIONS IN CASE OF PSYCHIATRIC CONSULTATION FOR COVID+ PATIENTS: TREATMENT OF DELIRIUM*

Introductory note:

Specific studies on Covid-19 delirium are not available .This document provides some information, not indications, and therefore has no guideline value. It has to be considered as a draft, issued in an emergency situation, which should be subject to additions or corrections as data and contributions will accumulate.

The choice of treatment must be based upon a careful evaluation of the patient (clinical conditions, concomitant treatments, individual characteristics)

Possible therapeutic options:

Dexmetodimin (for ICU patients): alpha 2 agonist, sedative-anxiolytic-analgesic that does not cause respiratory depression. Most frequent side effects: hypotension, hypertension and bradycardia (attention to interactions with beta blockers), which occur, connected, in about 25%, 15% and 13%of cases. D. is OK even in kidney failure. Caution should be observed in case of liver failure. D. is metabolized oxidatively by CYP2A6, CYP1A2, CYP2E1, CYP2D6 and CYP2C19. It is a CYP2B6 inhibitor and a possible inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP3A4 (but mainly in vitro studies). Attention must be payed because many of the antivirals are eliminated oxidatively, especially by CYP 450 3A4 AND 2D6. Dexmetodimin, therefore, limit the concentrations of antivirals. However, if it is used briefly, the effect should not be particularly pronounced.

Tiapride: useful if the patient is agitated (hyperkinetic delirium) and in therapy with Lopinavir / Ritonavir (Lo/Ri) . The dosage is in the range 50 mg - 300 mg in 24 hours. Tiapride is eliminated by

kidneys, therefore does not interfere with the CYP implicated in the metabolism of Lo / Ri and the most commonly used antibiotics. Tiapride can be administered orally, i.m. (if not clotting problems) and also i.v. (useful in cases of malabsorption). In case of hyperkinetic delirium, it can be started with 100 mg i.m., repeatable up to 3 times in the 24 hours. As soon as possible the drug should be administered orally, with concentration of dosage in the evening to promote the sleep-wake rhythm (e.g. 50 mg at 8 o'clock, 50 mg at 16 o'clock, 100 mg at 22 o'clock).

It is always necessary to evaluate the possible QTc prolongation, a risk to be weighed in the short term compared to the advantage of the sedative efficacy of the drug. The risk of arrythmias, especially in association with lopinavir, is present but remains relatively low. More attention is required for patients with hypokalaemia and hypomagnesaemia (e.g. due to vomiting and diarrhea). SatO2 should always be monitored for the risk of respiratory depression.
In “acute” use (24-48 hours), in case of poor response to Tiapride the use of **Promazine** i.m. may be taken into consideration (if not contraindicated for coagulation problems), with a dosage that can vary from 50 mg to max 300 mg/24 hours. Promazine is very strong anti-histaminic, low anti-alpha adrenergic and low anti-cholinergic agent. Cardiovascular risk (including hypotensive risk etc.) is lower than many of the other typical ones. Promazine has not pronounced sedative proprerties. However, attention should be given to the risk of respiratory depression. Interactions with Promazine (due to hepatic metabolism: CYP 1A2, 2C19 and 3A4) may exist (with Lo/Ri as regards to CYP 3A), but they are not so relevant if weighted on short-term use (3-4 days), also due to the very short (6 hours) half-life of the drug. It should be considered that Ritonavir inhibits CYP 3A4 and may increase the concentration of promazine. As regard to the most frequently used antibiotics, there are no significant interactions for Tazobactam, Piperacillin and Doxicillin (the latter with 50% hepatic metabolism), above all thanks to a mainly renal metabolism. As regard to Hydroxychloroquine (hepatic metabolism by CYP 2D6, 2C8, 3A4, 3A5) the interaction with Promazine is not such as to configure a net contraindication, at least in the short term. As with Tiapride, it is necessary to evaluate the possible QTc prolongation (for example, in association with lopinavir) and SatO2 must be monitored for the risk of respiratory depression (the is a relative risk in case of short-term administration). The risk of arrythmias in association with lopinavir remains relatively low. More attention is required for patients with hypokalaemia and hypomagnesaemia (e.g. from vomiting and diarrhea).

Aripiprazole: this SGA is useful for hypokinetic delirium. In hyperkinetic delirium, it is mainly useful in the immediate release intramuscular formulation (9.75 mg per IM vial). It has no anticholinergic activity and low anti-histaminergic activity. The risk of arrhythmias is also very low, as the risk of respiratory depression. Aripiprazole has a low risk of interaction (there is an increase in

concentration with CYP 2D6 and 3A4 inhibitors, but use of moderate doses is enough not to create problems; the maximum dosage allowed in the absence of CYP inhibitors is 3 fl per day, at intervals of minimum 2 hours).

Haloperidol is a drug very well studied in delirium. It has a low risk of respiratory depression. It has no anti-histamic and anticholinergic properties. Use of Haloperidol is associated with an increased risk of arrhythmias, due to prolongation of QTc and repolarization interval, dystonia, and epileptic seizures from lowering the epileptogenic threshold. Problems may be arise from dystonic/ neurodisleptic crises.

Benzodiazepines should be avoided unless delirium tremens is suspected**.**

Note for patients treated with Tocilizumab: Cytochrome P450s are inhibited by infections and inflammations, including those mediated by interleukins through IL-6. IL-6 inhibition induced by Tocilizumab can therefore re-potentiate cytochrome by increasing its effectiveness.

(* this contribution is due to Fabrizio Pavone and Andrea Fagiolini)

INDICATIONS ON THE USE OF PSYCHOTROPIC DRUGS IN PATIENTS COVID+**

Methodological annotations

This working group used the "rapid review" method to analyze the scientific literature, the main pharmacological databases, and the documents produced by the most important scientific associations, in order to generate practical indications on the rational use of psychotropic drugs in patients with COVID -19.

Clinical results and annotations

The search results are shown in the table on the following page. This table cannot be considered exhaustive and will be subject to periodic updates. To complete what is shown in the table, the following aspects must be taken into consideration:

1. Other drugs commonly used in patients with COVID-19 infection have not been reported, as interactions with psychiatric drugs are likely to be negligible. These include: acetylcysteine, oral or inhaled corticosteroids, some antibiotics (in particular ceftriaxone, amoxicillin / clavulanic acid, piperacillin / tazobactam), tocilizumab.

2. Benzodiazepines can cause respiratory depression both by central action (depression of the bulbar respiratory centers; more at risk those mostly sedative) and peripheral (muscle relaxant action).
3. Generally BDZ should be avoided in patients at high risk of impaired respiratory performance. If it is considered clinically necessary, prefer the use of BDZ with short half-life.
4. Antipsychotics, especially the most sedative ones, and even more the association of antipsychotics, may increase the risk of respiratory depression.
5. The prolongation of the QTc is possible both with chloroquine / hydroxychloroquine, and with some antibiotics. Among antipsychotics it is therefore preferable to avoid haloperidol and prefer drugs with lower risk of QTc prolongation.
6. Considered the QTc prolongation problems with some antipsychotics sedatives and the problem of respiratory compromission with benzodiazepines, to induce rapid sedation it could be useful to resort to:
    a) Thiapride (Sereprile): for hyperkinetic delirium, and potentially also for important states of anxiety. Range: 50-300 mg / day. Available formulations: tablets 100 mg; ampoules 100 mg / 2 mL fL IM or EV;
    b) Aripiprazole (Abilify) solution for injection IM 1.3 mL 7.5 mg / mL: up to 3 ampoules per day in case of hyperkinetic agitation / delirium.

*(** This contribution is due to Giovanni Ostuzzi, Francesco Amaddeo, Giulia Michencigh, Andrea Fagiolini; Giuseppe Imperadore Corrado Barbui)*

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	Sedazione	Lopinavir/Ritonavir	Clorochina/idrossiclorochina	Antibiotici più utilizzati*	Note
BENZODIAZEPINE					
Etizolam	+	↑ ETI via CYP3A4			Emivita <6h
Triazolam	++	↑ TRI via CYP3A4			Emivita <6h
Zolpidem	++	↑ZOL via CIP3A4		↑ZOL con CLR via CYP3A4	Emivita <6h
Bromazepam	+	↑ BRO (lieve)			Emivita 10-20h
Lormetazepam	+++				Emivita 10-20h
Lorazepam	++				Emivita 6-20h
Delorazepam	++	↑ DEL via CYP3A4			Emivita 6-20h
Alprazolam	+	↑ ALP via CYP3A4			Emivita 6-20h
Diazepam	++	↑ DIA via CYP3A4			Emivita >20h

Flurazepam	+++	↑ FLU via CYP3A4			Emivita >20h
Clonazepam	+++	↑ DIA via CYP3A4			Emivita >20h
ANTIDEPRESSIVI					
Sertralina		↑ SER via CYP3A4		↑ SER via CYP3A4 con CLR	
Citalopram		↑ CIT via CYP3A4	↑ QTc	↑ QTc con AZI e CLR	
Escitalopram		↑ CIT via CYP3A4	↑ QTc	↑ QTc con AZI e CLR	
Paroxetina	+	↑ PAR via CYP2D6	↑ PAR via CYP2D6 (lieve)	↑ QTc con SULF e AZI (lieve); ↑ PAR via CYP3A4 con CLR	
Mirtazapina	+++	↑ MIR via CYP3A4		↑ MIR via CYP3A4 con CLR	
Bupropione		↓ BUP via CYP2B6	↑ CLOR via CTP2B6		
Vortioxetina		↑ VOR via CYP2D6			
Venlafaxina		↑ VEN via CYP3A4	↑ QTc	↑ QTc con SULF, TRIM, AZI (lieve) e CLR; ↑ VEN via CYP3A4	
Duloxetina		↑ DUL via CYP2D6	↑ DUL via CYP2D6		
Amitriptilina	+++	↑ AMI via CYP3A4		↑ QTc con SULF, TRIM, AZI, CLR	
Trazodone	+++	↓ RITONAVIR via MDR1; ↑ TRA via CYP3A4		↑ QTc con SULF, TRIM e AZI; ↓ TRAZ con SULF (lieve); ↑ TRAZ via CYP3A4 con CLR	
Clomipramina	++	↑CLOM via CYP2D6; ↑QTc	↑QTc	↑QTc con AZI, CLR, SULF e TRIM	
ANTIPSICOTICI					
Tiapride	++		↑ QTc	↑ QTc con SULF, TRIM, AZI	Metabolismo renale. Uso EV consentito.
Aloperidolo	+	↑ ALO via CYP2D6; ALO+RITONAVIR ↑ QTc	↑ ALO via CYP2D6; ↑ QTc	↑ QTc con SULF, TRIM, AZI, CLR	
Promazina	+++	↑ PRO via CYP2D6	↑ PRO via CYP2D6; ↑ QTc	↑ tossicità del SULF; ↑ QTc con SULF, TRIM, AZI, CLR	
Clorpromazina	+++	↑ CLOR via CYP2D6	↑ CLOR via CYP2D6; ↑ QTc	↑ QTc con SULF, TRIM, AZI, CLR	
Clotiapina	+++		↑ QTc	↑ QTc con SULF, TRIM, AZI	
Risperidone	+	↑ RIS via MDR1	↑ RIS via CYP2D6 (lieve)	↑QTc con SULF, TRIM, AZI e CLR (lieve)**	
Paliperidone	+				Metabolismo renale
Olanzapina	++	↓ OLA	↑ QTc**	↑ QTc con CLR (lieve) **	
Quetiapina	++	↑ QUE via CYP3A4; ↑ QTc	↑ QTc	↑ QTc con AZI e CLR; ↑QUE con CLR	
Aripiprazolo		↑ ARI via CYP3A4	↑ ARI via CYP2D6 (lieve)	↑ QTc con AZI** ↑ ARI via CYP3A4	
Pimozide	+	↑QTc	↑ QTc	↑PIM via CYP3A4 con CLR, AZI ↑QTc con CLR e SULF	
Lurasidone	+	↑ tossicità LUR via CYP3A4		↑ LUR via CYP3A4 con CLR	
Clozapina	+++	↑QTc	↑rischio agranulocitosi; ↑QTc; ↑CLO (lieve)	↑QTc con AZI; ↑rischio agranulocitosi con SULF; ↑CLO con CLR (lieve)	
Asenapina	+	↑QTc	↑QTc	↑QTc con AZI, CLR e SULF	
STABILIZZATORI					
Pregabalin	+				
Valproato sodico	+	↓VALP (lieve)		↑ SULF (lieve)	
Litio		↑QTc	↑QTc	↑QTc con CLR e SULF (lieve)	
Carbamazepina		↓LOPINAVIR e ↑CARB via CYP3A4		↑ tossicità CARB; ↓SULF e TRIM	
Lamotrigina		↓LAM			
Gabapentin	+				

* Abbreviazioni: sulfamethoxazole (SULF); trimethoprim (TRIM); azithromycin (AZI); clarithromycin (CLR)

** Secondo le linee guida Maudsley il rischio di prolungamento del QTc è basso per RIS, PALI, OLA e verosimilmente nullo per ARI e LUR.**

Secondo le linee guida Maudsley il rischio di prolungamento del QTc è basso per RIS, PALI, OLA e verosimilmente nullo per ARI e LUR.