Review Article

Initial medical work-up of first-episode psychosis: a conceptual review

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Abstract

Aim: To help clinicians carry out a comprehensive, medical diagnostic assessment in first-episode patients who are suspected of developing schizophrenia.

Methods: Conceptual review of the published work with emphasis on the diagnostic goals of excluding medical causes of psychosis and establishing a medical baseline.

Results: There is no agreed-upon standard for the initial medical work-up of first-episode cases. Excluding secondary causes of schizophrenia requires consideration of likelihood of disease; laboratory test performance; and relevance of positive test results.

Conclusions: We propose a medical work-up for first-episode psychosis that combines: (i) broad screening; (ii) exclusion of specific diseases informed by treatability and epidemiology; and (iii) medical baseline measures.

Key words: first-episode psychosis, medical work-up, secondary schizophrenia.

> Vor die Therapie haben die Götter die Diagnose gestellt.
> (The Gods have put diagnosis before treatment.)
> – time-honoured medical adage

INTRODUCTION

Over the last decade, first-episode schizophrenia has become the focus of much clinical attention, particularly with regard to early intervention and treatment.[1] However, although many schizophrenia guidelines can be consulted,[2] they mostly focus on treatment, with less emphasis on diagnosis. Specifically, there is no agreed-upon standard for what constitutes a comprehensive, medical diagnostic assessment of a patient who has a first episode of psychosis, suspected to represent beginning schizophrenia. When we recently sampled clinicians who attended the symposium, 'Treating Patients Early: Update on the Controversy' at the 2008 annual meeting of the American Psychiatric Association (APA) about their use of three selected tests for the work-up of first-episode psychosis (i.e. brain imaging, electroencephalogram and HIV), answers varied widely. We included the answers from those who responded (ranging from 338 to 361 participants) in Table 1 and contrast them with a summary of current guideline recommendations from three professional organizations (see references[3–5] in Table 2).

Such differing opinions suggest that there is no single, right approach, and we are not proposing one. Hence, the goal of this conceptual review is not to advocate for one screening battery or to provide a review of all possible causes for psychosis but to help clinicians investigate a patient who has what appears to be a first episode of schizophrenia by

TABLE 1. Responses to three audience questions of about 700 clinicians who attended the symposium, 'Treating Patients Early: Update on the Controversy' at the 2008 annual meeting of the American Psychiatric Association (APA) regarding their use of selected tests for the work-up of first-episode psychosis

(1) Do you routinely order an EEG as part of a first-episode evaluation?	
No	63%
Yes	37%
(2) Which neuroimaging test do you routinely order as part of a first-episode psychosis evolution?	
None	37%
Computed tomography	32%
MRI without contrast	19%
MRI with contrast	10%
SPECT	2%
(3) Do you routinely order HIV testing as part of a first-episode psychosis evaluation?	
No	79%
Yes	21%

EEG, electroencephalogram; MRI, magnetic resonance imaging; SPECT, single photon emission computed tomography.

TABLE 2. Summary of current guideline recommendations from three professional organizations regarding the initial work-up of first-episode psychosis

	APA 2004[3] USA	CPA 2005[4] Canada	RANZCP 2003[5] Australia and New Zealand
Physical exam (PE)	Complete PE including neurological exam	PE including neurological exam	Neurological exam
	Vital signs	Vital signs	
	Weight and height//BMI	BMI, waist circumference	Weight/BMI
Routine laboratory tests	CBC, electrolytes, BUN/creatinine, liver function tests	CBC, electrolytes, renal and liver function tests	
	Thyroid function tests	Thyroid function tests	
	Pregnancy test (women of child-bearing age)		
Ancillary tests	Test for syphilis	Syphilis test	
	Hepatitis C if clinically indicated	Hepatitis tests, if indicated	
	HIV, if clinically indicated	HIV test, if indicated	
	Urine toxicology screen	Toxicology screen	
	Heavy metal screen, if clinically indicated		
Neuroimaging	MRI or CT, if clinically indicated (MRI preferred over CT)	CT or MRI should be carried out	CT
EEG	EEG, if clinically indicated		
Genetics		22q11 deletion syndrome, as clinically indicated	
Medical monitoring	Fasting blood glucose, lipid panel	Fasting plasma glucose, lipid panel	Fasting serum glucose
	ECG, if clinically indicated	ECG	ECG
	Prolactin level, if indicated by history	Prolactin level where clinically indicated	
	Clinical assessment of EPS and abnormal movements	Assess for EPS	Neuro-exam for movement disorders
	Ocular exam, if indicated	Ocular exam	
	Consider preventive health care		

APA, American Psychiatric Association; BMI, body mass index; BUN, blood, urea, nitrogen; CBC, complete blood count; CPA, Canadian Psychiatric Association; CT, computed tomography; ECG, electrocardiogram; EEG, electroencephalogram; EPS, extrapyramidal symptoms; MRI, magnetic resonance imaging; RANZCP, Royal Australian and New Zealand College of Psychiatrists.

thinking through the logic of ordering *and not ordering* particular tests. The old clinical wisdom that 'diagnosis guides treatment guides prognosis' reminds clinicians that the medical approach (defined as an approach to clinical problems that stresses diagnosis and differential diagnosis as well as the provision of care derived from this process) derives its strength from correctly diagnosing patients so that the most effective treatment can be selected. We will focus on the initial diagnostic

phase of probable schizophrenia with regard to excluding medical causes for psychosis (the sine qua non of any psychiatric diagnosis), and identifying medical morbidity. Although our discussion is based on experience with patients with psychosis in the USA or similar settings, the general principles will apply to other locales as well.

INITIAL DIAGNOSTIC GOALS

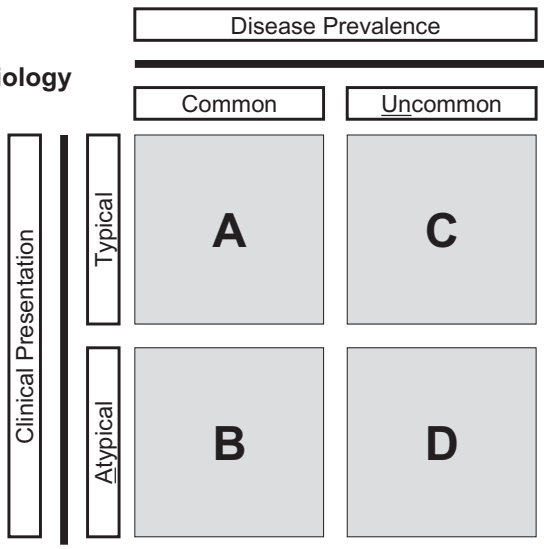
Families and physicians are invested in a timely diagnosis of a schizophrenia-spectrum disorder (i.e. schizophreniform disorder, schizophrenia or schizoaffective disorder) to initiate appropriate acute treatment (i.e. initiation of an antipsychotic) and set the stage for the appropriate, schizophrenia-specific long-term interventions (i.e. antipsychotic maintenance treatment and psychosocial rehabilitation). Making a diagnosis of a likely schizophrenia-spectrum disorder as early as possible and reducing the time until treatment with an antipsychotic is initiated (i.e. reducing the duration of untreated psychosis) holds the promise of improving long-term outcomes.[6,7] As the diagnosis of schizophrenia hinges on the presence of a typical clinical picture *in the absence of a medical condition that could account for the observed and experienced psychopathological signs and symptoms, respectively*, an 'organic' work-up is an integral part of this diagnostic phase. Once schizophrenia is diagnosed, treatment will invariably involve the use of antipsychotics and other psychotropics. A medical baseline needs to be established to assure that medications can be given safely in the short run. In addition, a medical baseline sets the stage for long-term follow up and allows for monitoring of iatrogenic morbidity, particularly movement disorders and metabolic problems. All three guidelines clearly advocate both goals (i.e. the exclusion of medical causes of psychosis and a medical baseline assessment), albeit with varying degree of detail (see Table 2).

However, choosing appropriate screening tests to accomplish both goals meets with conceptual problems, which we will discuss first before moving to reviewing the pros and cons of specific tests for a diagnostic, medical work-up.

PROBLEMS EXCLUDING SECONDARY CAUSES OF PSYCHOSIS

When approaching the medical differential diagnosis of a patient with psychosis, a clinician faces three problems: creating a manageable list of relevant diseases to exclude; choosing the appropriate tests to rule-in or rule-out diseases; and judging the relevance of a positive test result.

FIGURE 1. Schematic breakdown of potential causes for psychosis (ψ) by disease prevalence and clinical presentation to illustrate the diagnostic challenge of first-episode psychosis.
Examples:
Cell A denotes common diseases where psychosis is typical (i.e. a presenting and characteristic symptom) (e.g. primary psychotic disorders themselves and drug-induced psychosis).
Cell B denotes diseases that are common but where psychosis is rarely a presenting feature (e.g. stroke, HIV).
Cell C denotes uncommon diseases (rare diseases or diseases rarely encountered in a particular treatment setting) that include psychosis in their classic presentation (e.g. maladie du sommeil).
Cell D denotes uncommon diseases where psychosis is possible but not characteristic (e.g. adult-onset genetic syndromes such as Niemann–Pick's disease).



Problem #1: the prevalence/rarity problem

One obvious problem facing a clinician is the huge variety of medical diseases and toxins that can potentially present with psychosis (for a tabulated list, see Freudenreich *et al.*[8]). A breakdown of potential causes for psychosis by disease prevalence (indicating how familiar the clinician will be with the disease) and clinical presentation (with regard to propensity of psychosis to be part of the clinical syndrome) as shown in Figure 1 illustrates the diagnostic challenge graphically. (The relevant diseases for each cell will depend on the country and treatment setting.)

Common diseases with typical presentations (i.e. psychosis as an expected feature of the presentation) should allow for a quick and accurate working

diagnosis. In most settings, this cell (Cell A) will contain mostly drug-induced psychoses and the primary psychotic disorders themselves once a delirium has been excluded. Many fairly common medical diseases, however, can potentially present with psychosis although this would be clinically atypical (Cell B). For example, a manic patient with psychosis presenting in Uganda could be suffering from HIV-related secondary mania[9] even though the majority of HIV patients do not have psychosis. Similarly, although a stroke can lead to psychosis, this outcome is rare.[10] Although clinicians will be familiar with the disease, they might not be familiar with psychosis as part of the syndrome. Psychiatric disorders themselves can be atypical as well, particularly with regard to age of onset and symptom picture. Uncommon diseases with typical (or even 'classic') presentations (Cell C) pose significant challenges as clinicians might have never seen the disease or have limited experience with it. Some diseases will be uncommon in general (e.g. acute intermittent porphyria), some uncommon in certain geographic areas (e.g. maladie du sommeil or sleeping sickness caused by the protozoan, trypanosoma gambiense will be uncommonly encountered in North America but not in West Africa). Psychiatrically, some culture-bound syndromes fall into this category (e.g. bouffée délirante as an example of an acute-onset psychotic syndrome without a prototypical prodrome). Rare disorder with atypical presentations (Cell D) will only be diagnosed by astute clinicians who remain vigilant and informed (e.g. genetic syndromes that can also have an adult onset, such as Niemann–Pick's disease[11] and Tay-Sachs disease;[12] or newly delineated syndromes, such as paraneoplastic syndromes related to antibodies to *N*-methyl-D-aspartate receptors[13,14]).

To put the above discussion in perspective, we can look at data from the seminal Northwick Park First-Episode study in the UK.[15] Among 268 patients between the ages of 15 and 70 referred for a suspected first episode of schizophrenia (i.e. not suspected of suffering from an 'organic' syndrome), 9 (3%) were subsequently discovered to have clear-cut 'organic' disease. In this cohort, there were three patients of neurosyphilis, two patients of neurosarcoidosis, one lung cancer, one autoimmune multisystem disease, one patient of cerebral cysticercosis and one patient of thyrotoxicosis. Although the specific causes will undoubtedly vary in other cohorts, 3% can serve as a benchmark incidence for expected medical causes for psychosis in Western countries.

Problem #2: test performance

To avoid missing medical diagnoses, physicians might be inclined to order screening tests. However, all tests are inherently imperfect in that no test has 100% sensitivity or specificity. Test performance in the real world depends on the prevalence of the disorder under investigation.

Taking test characteristics into account, general principles apply when making a decision with regard to ordering any test in the work-up of first-episode patients:

1 The predictive values of any test depend on the disease prevalence (Bayes' theorem of conditional probabilities): indiscriminate screening for a disease that is not clinically suspected is particularly unwise if a disease is rare as positive test results will most likely represent a false-positive test. Put differently, testing for rare diseases is most useful if the disease is clinically suspected (i.e. if there is a high pretest probability). Clinical judgement, however, is required to decide when a false-positive result (obtained with an inexpensive screening test) outweighs the risk of missing a disease altogether.
2 A useful distinction can be drawn with regard to the purpose of a test, whether a test is ordered to rule in a suspected disease or to rule one out.[16]
   - Rule-in tests. Such tests should have high specificity and should be ordered to confirm a disease. If positive, you will keep the disease on your differential list. Some diagnoses can be very difficult to make if no good rule-in test exists (e.g. a test is somewhat specific but has low sensitivity); in such circumstances, a diagnosis must be actively pursued (e.g. serial electroencephalograms (EEGs) to confirm a clinically suspected diagnosis of epilepsy; adding 24-h urine copper if Wilson's disease is suspected despite normal ceruloplasmin level).
   - Rule-out tests. It is very important that such tests, which are often screening tests, have a very high sensitivity (i.e. have a low rate of false negatives) for if such a test is negative, you will remove the disease from your differential list. A highly sensitive test that is negative is reassuring regarding the absence of disease; normal magnetic resonance imaging (MRI) and negative HIV test are examples of reassuring test results of highly sensitive tests. The serum rapid plasma reagin is an example of a less than ideal screening test as it can be negative in late-stage infections, the stage of interest in psychotic patients suspected of neurosyphilis.

Problem #3: comorbidity and causality

Discovering a medical disease in a patient with psychosis leads to the question of relevance: is the disease aetiologically or pathophysiologically relevant with regard to psychosis? Slater was one of the first to systematically examine the question of causation in comorbid conditions in an influential essay on the relationship between epilepsy and schizophrenia.[17] He differentiated between three theoretical levels of causation: epilepsy and psychosis representing mere chance combinations; epilepsy precipitating genuine schizophrenia; or a schizophrenia-like illness being purely epileptogenic in origin. Given our lack of knowledge about the aetiology and pathophysiology of schizophrenia, the role of comorbid conditions is often less than clear. Using Slater's organizing scheme, drug use could be incidental; it might precipitate 'genuine' schizophrenia in vulnerable individuals; or it might be solely responsible for the psychosis and resolve completely if drug use ceases. Further complicating this problem, different relationships could be true in different patients.

Even if a discovered disease is not thought to be aetiologically relevant, it could still be important to diagnose. Alvan Feinstein, the father of clinical epidemiology,[18] added to our understanding of such aetiologically unrelated yet important, 'true' comorbidity. Using cancer as a model, he showed that the presence of comorbidity that was not a feature of the cancer itself influences the natural history of cancer and in that way impacts prognosis.[19] In schizophrenia, comorbid conditions such as smoking or the metabolic syndrome that are not features of schizophrenia itself not only complicate psychiatric management but they have a profound impact on the prognosis quo ad vitam, just as in cancer. Other than suicide, preventable medical disease-related mortality is responsible for the reduced life expectancy in schizophrenia patients compared with the general population.[20,21] It is this latter point that justifies a thorough medical baseline assessment.

DIAGNOSTIC MEDICAL WORK-UP

Exclusion of medical causes of psychosis

As the preceding section has shown, accomplishing the first goal of a medical work-up, excluding all potential medical causes for psychosis, is conceptually impossible, let alone pragmatically not feasible. To solve this dilemma and deal with the fear of missing a treatable disease, clinicians can choose between two different work-up philosophies: an academic approach that is guided by the ideal of a comprehensive differential diagnosis and the systematic exclusion of possible diseases, requiring extensive screening; and a pragmatic approach that takes into account the natural history of most illnesses (i.e. to eventually declare themselves) and cost. Several authors have argued for more extensive screening than commonly offered, both in general[22] and specifically for metabolic disorder.[23] Based on a review of the published work, Coleman and Gilbert[24] have assembled an extensive list of diseases that can potentially present with psychosis and put together suggestions for screening batteries. Conceptually, they are correct in their argument that we can only extend the phenotype of some medical diseases (in this case diseases presenting atypically with psychosis) if we look for them. However, apart from the feasibility in many treatment settings, the yield of such an extensive work-up has not been empirically validated, particularly as most diseases can be expected to eventually declare themselves with ancillary signs or symptoms beyond psychosis.

The two philosophies must not be mutually exclusive, and a feasible laboratory test battery can be constructed that contains some element of broad screening, plus the exclusion of specific disorders informed by treatability and epidemiology. If necessary, the initial work-up can even be pared down and extended later if the clinical picture changes, particularly if non-response develops or the clinical picture changes. This latter scenario assumes that long-term follow up is possible.

What screening laboratory battery?

Few would argue against obtaining a complete blood count, electrolytes (including calcium) as well as tests of kidney function and liver function to establish the absence of gross organ failure. The value of urine drug screening is also undisputed. Although of unproven utility, we propose to include two broad, non-specific markers of inflammation (i.e. erythrocyte sedimentation rate and antinuclear antibody) to broadly screen for inflammatory and rheumatologic disorders. In addition, several specific diseases should be excluded, particularly conditions that are highly treatable but that might not be apparent clinically unless tested for, including thyroid disease (i.e. thyroid-stimulating hormone), Wilson's disease (i.e. ceruloplasmin level), pernicious anaemia (i.e. vitamin B12) and two infections, neurosyphilis and HIV. Guidelines identify neurosyphilis and HIV as specific diseases to screen for (in the presence of risk factors). Interestingly, HIV

testing was only routinely offered by a minority of APA attendees. We see this as problematic as HIV can present with psychosis, is prevalent, easily diagnosable and treatable. Of note, the Centers for Disease Control has recently recommended universal screening without regard to risk factors.[25] (State laws must be followed, and not all states allow opt-out testing (i.e. a test will be carried out unless explicitly refused) but require consent, including written consent before testing.) Although the rapid plasma reagin is often reflexively ordered to screen for neurosyphilis, more sensitive (and specific treponemal-specific tests are increasingly used for syphilis screening (http://www.cdc.gov/std/treatment/2006/toc.htm). A negative FTA-ABS (fluorescent treponemal antibody absorbed) which has a sensitivity of 97% in patients of neurosyphilis argues strongly against exposure to syphilis.[26]

Any additional tests should be guided by the clinical picture itself, family history and epidemiological considerations. For example, a lumbar puncture should be offered if infectious processes are a clinical consideration and serum alone is inadequate to establish a diagnosis. A chest X-ray would be indicated if there is suspicion of sarcoidosis or a paraneoplastic syndrome in a smoker. Urine testing for heavy metals is specifically mentioned in the APA guideline (e.g. if work environment suggests exposure to toxins).

Currently, routine genetic testing is not recommended in schizophrenia unless individual features or a family history suggests the presence of a genetic syndrome. The only guideline that addresses genetic testing is the Canadian Schizophrenia Guideline, which recommends fluorescent *in situ* hybridization testing for chromosome 22q11 deletion or velocardiofacial syndrome if certain clinical features are present. Such clinical red flags include childhood learning difficulties or low IQ; a history of midline defects (e.g. cleft lip or palate); cardiac abnormalities; dysmorphic features (e.g. long face with prominent upper jaw, flattening of the cheeks, underdeveloped lower jaw or prominent nose with narrow nasal passages); or a history of recurrent ear infections or hearing loss. In a cohort of 634 Israeli schizophrenia patients, approximately 1% of patients were carrying the 22q11 deletion.[27] Cytogenetic testing should be considered in patients with childhood-onset schizophrenia and associated cognitive or developmental problems as a higher rate of genetic problems can be identified in such patients.[28] However, genetic testing is only clinically useful if the discovery of a genetic syndrome leads to further testing for and treatment of medical conditions associated with the syndrome or genetic counselling.

TABLE 3. Indications for ordering an electroencephalogram for the work-up of first-episode psychosis

Any documented seizure history†
History suggestive of ictal evens (e.g. episodic loss of consciousness, staring spells)†
Serious past head injury†
Uncooperative patient with confusion
Suspicion of narcolepsy (i.e. hallucinations occurring at sleep–wake cycle transitions)‡

†Sleep-deprived electroencephalogram preferred.
‡Requires Multiple Sleep Latency Test.

How useful is an EEG?

In clinical practice, a random EEG is frequently obtained in the work-up of first-episode psychosis; 37% of APA participants did so. This is a problematic practice as an EEG is neither sensitive nor specific. George Murray, MD summarizes the sensitivity problem the following way: 'If you go fishing and you don't catch anything, you do not conclude that there are no fish in the ocean' (Dr George Murray, pers. comm., 1999). In their classic study, Salinsky and colleagues showed that serial, sleep-deprived EEGs are often necessary to support a clinical diagnosis of epilepsy (with a positive EEG showing interictal epileptiform activity), with diminishing returns after three or four negative EEGs.[29] Of note, in their cohort of 429 referred epilepsy patients, only 59% had a positive EEG. EEG specificity is also problematic. Manchanda and colleagues[30] reported that 17% of 122 first-episode patients had a clearly arrhythmic EEG. Although a arrhythmic EEG is a bad prognostic sign with regard to symptom remission in first-episode patients,[30,31] such 'biomarkers of doom' are not useful in treatment selection. Another confound are medication-induced EEG changes. For example, in a prospective trial of 50 chronic schizophrenia patients who were switched from haloperidol or fluphenazine to clozapine, 53% developed EEG changes, including spike/sharp activity in 13%.[32]

In summary, although an EEG is useful to confirm a seizure disorder when the clinical situation suggests one (see Table 3 for EEG indications), there is no clear advantage of ordering EEGs routinely. If an EEG is ordered because of suspected seizures, the EEG should be sleep-deprived (best if patient actually falls asleep) to increase the likelihood of EEG abnormalities and it might have to be repeated; Holter-EEG monitoring might be necessary in some patients to establish a diagnosis of epilepsy. Note that narcolepsy that can be confused with schizophrenia[33] is not diagnosed with a routine EEG

but requires a Multiple Sleep Latency Test. None of the guidelines recommends a screening EEG.

How useful is neuroimaging?

To judge the value of brain imaging, it helps to know the expected base rate of abnormal neuroimaging finding in the general population. Katzman and colleagues examined 1000 MRIs from normal, healthy persons who served as controls in various research studies (mean age 55 years).[34] Although 82% of scans were normal, 18% were considered abnormal (15.1% incidental, not requiring follow up; 1.8% requiring routine referral; and 1.1% requiring urgent referral, mostly for brain tumours). Rates very similar to this base rate, with 78% normal and 22% abnormal MRIs, were found in a cohort of 152 first-episode patients (mean age 22 years) who had an MRI carried out as part of a baseline evaluation.[35] Although 13/152 patients (8%) were in need of referral for further evaluation, only 2/152 (1.3%) were judged to have a disease aetiologically related to psychosis (demyelination in both patients). The results for routine computed tomographies are comparable to MRI with regard to focal lesions. For example, in one study of 127 healthy, young military recruits, only four scans (3%) were found to show incidental abnormalities.[36] In another cohort of 168 first-episode psychosis admissions who underwent computed tomography scanning, focal findings were present in 6.6% of patients.[37] However, non-specific ventricular and cortical enlargement was noted in up to 40% of patients. Although statistically associated with a worse prognosis, such a 'biomarker of doom' (cf. EEG) is not useful for clinical decision-making for individual patients.

Thus, the yield of neuroimaging in prototypical first-episode patients (i.e. young, medically healthy cohort with no clinical indication for suspected 'organic' pathology) is going to be low, albeit not zero, and a clinically important medical disease can be expected for perhaps 8% of patients (although disorders of aetiological relevance are probably much less likely). The most likely findings are developmental abnormalities without any clinical significance but in some rare instances metabolic disorders affecting the white matter can be picked up.[38] Nevertheless, even a negative scan is valuable, and the most important argument for routine brain imaging of first-episode patients is perhaps this: a negative scan establishes the 'functional' character of the psychosis and can help patients and families towards acceptance of a psychiatric disorder. For a compilation of pros and cons of routine imaging screening see Table 4.

TABLE 4. Arguments for and against the CT/MRI in the work-up of first-episode psychosis

Arguments against:
Many incidental findings
Abnormal finding does not establish causality
Low yield
Arguments for:
MRI can substitute for other screening (e.g. temporal lobe sclerosis of epilepsy; metabolic disorders affecting white matter)†
Medico-legal (missed brain tumour)
Baseline for chronic disorder
Negative CT/MRI provides reassurance and support of diagnosis of schizophrenia

†Not been empirically validated.
CT, computed tomography; MRI, magnetic resonance imaging.

The majority of the APA audience endorsed some form of routine neuroimaging, as do two of the three guidelines. If brain imaging is offered, we agree with the APA guideline that an MRI should be the preferred imaging method as it is more sensitive to detect those lesions of interest that are associated with psychosis (i.e. white matter diseases; brain tumours; temporal lobe abnormalities including sclerosis associated with temporal lobe epilepsy).

Medical baseline assessment

In addition to excluding medical disorders as a proximate cause of psychosis, establishing the presence of relevant medical comorbidities is the second goal of the medical work-up.

Comorbid medical disorders relevant for the psychiatrist and hence particularly important to identify in the beginning of treatment are those that influence the initial dose and choice of treatment with regard to immediate safety (e.g. normal renal and liver function; excluding cardiac disease with an electrocardiogram (ECG); and excluding pregnancy with a pregnancy test).

In addition, as for most patients with schizophrenia, physical health problems compounded by iatrogenic complications are a strong possibility, establishing a medical baseline is crucial. Such a baseline allows for proactive monitoring and at least secondary prevention of antipsychotic-induced medical problems. The goal is to reduce long-term morbidity and mortality. A broad consensus about the need for longitudinal physical health monitoring has emerged.[39–41] All guidelines focus on two areas (with regard to iatrogenic morbidity from antipsychotics): movement disorders and metabolic problems. A physical examination with emphasis on

neurological abnormalities, weight and height (to calculate body mass index) and waist circumference as well as fasting glucose and lipid profile will establish a comprehensive baseline that allows for the early recognition of abnormal movements and metabolic problems. Guidelines do not suggest checking prolactin levels unless a patient has symptomatic hyperprolactinaemia. There is currently no consensus about the value of diagnosing asymptomatic antipsychotic-induced hyperprolactinaemia despite possible long-term health consequences (e.g. osteoporosis).[42] A prolactin level for all patients on prolactin-elevating antipsychotics would establish if hyperprolactinaemia is in fact present, giving patients the chance to make an informed decision regarding switching to a prolactin-sparing antipsychotic. In healthy, young adults, an ECG and an eye exam are unlikely to be abnormal; an ECG should probably be obtained routinely to guard against sudden cardiac death. Other health screening can easily be added if clinically indicated (e.g. screening for hepatitis C if injection drug use). The role of the psychiatrist continues to be defined with regard to the extent of responsibility for routine medical care of psychiatric patients.[43]

TABLE 5. Medical work-up for first-episode psychosis

Physical exam with emphasis on neurological exam
Vital signs
Weight and height (BMI), waist circumference
ECG (if cardiac risk)
Laboratory tests
Broad screening and medical baseline:
CBC
Electrolytes including calcium
Renal function tests (BUN/creatinine)
Liver function tests
Erythrocyte sedimentation rate
Antinuclear antibody
Fasting glucose
Lipid profile
Consider prolactin level
Consider hepatitis C (if risk factors)
Pregnancy test (in women of child-bearing age)
Urine drug screen
Exclude specific treatable disorders:
TSH
FTA-ABS (fluorescent treponemal antibody absorbed)
HIV test
Ceruloplasmin
Vitamin B12
Neuroimaging
MRI (preferred over CT)
Ancillary tests
Expand aetiological search if indicated, taking into account epidemiology:
For example, CXR, EEG, lumbar puncture, karyotype, heavy metal testing
Expand medical monitoring if indicated:
For example, eye exam (if risk factors for cataracts)

BMI, body mass index; BUN, blood, urea, nitrogen; CBC, complete blood count; CT, computed tomography; CXR, chest X-ray; ECG, electrocardiogram; EEG, electroencephalogram; MRI, magnetic resonance imaging; TSH, thyroid-stimulating hormone.

SUMMARY

A focused medical work-up that accomplishes our two diagnostic goals (i.e. excluding medical causes of psychosis and establishing a medical baseline) is proposed in Table 5. The choice of tests was guided by an acknowledgment of the difficulties as outlined in this paper, particularly that the most comprehensive battery of diagnostic tests is not necessarily the best one: screening indiscriminately for rare disorders predictably results in too many false-positive tests. Also, for suspected disorders, a negative test could be false negative, and such diagnoses must be actively pursued. Local considerations (e.g. infectious diseases endemic to area) and individual-specific attributes (e.g. work place exposure to toxins) are important considerations in selecting the most appropriate laboratory tests. And finally, the role of aetiology in comorbid conditions cannot always be fully elucidated. Perhaps the best assurance against missed medical diagnoses is long-term follow up and a willingness to revisit the issue of screening in patients who are refractory to treatment or if the clinical picture changes. The National Institute for Clinical Excellence Schizophrenia Guideline from the British National Health Service (available at http://www.nice.org.uk/Guidance/CG1) recommends supporting referral for a second opinion in view of the significant uncertainty and long-term ramifications after a first episode of psychosis and possible diagnosis of schizophrenia. Such specialist referrals can include a review of the adequacy of the initial medical work-up.

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