# Psychopharmacological Treatment

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## Introduction

What is the role of pharmacotherapy in the process and attainment of recovery? There is quite a spectrum of opinions on the effect of psychopharmacological agents on individuals ranging from the writings of Patricia Deegan in reference to her own early negative experiences, to multiple reviews and practice algorithms that discuss the virtues of antidepressants, antipsychotics, and mood stabilizers in their role in stabilization and maintenance of psychiatric symptoms in severe mental illness. Deegan (2007) described the abject hopelessness she felt when she was told by her psychiatrist that she had a "chronic lifelong illness" from which there was no recovery. Instead of viewing the antipsychotics prescribed to her as a panacea, she found them "noxious" and "dangerous" and likened the side effects to, "walls as thick and impenetrable as any institution" and leaving her "isolated and alienated." In describing her first hospitalization, Houghton (1982) likened her confinement to an "entombment" and the medications as the "embalmment" as she "walked among the dead."

That is not to say that those involved in the recovery movement think that psychotropic medications are needless. Actually, great strides toward obtaining recovery for many suffering from severe mental illness are due, in fact, to advances in pharmacotherapy over the past few decades. For these people, medications have paved the way for utilizing other treatment modalities in obtaining symptom remission and improvement of functional status. There have been descriptions of the changes in "mind, body, and social experience" that occur with illness, and the subsequent treatment that helps the person take control, reinforcing her ability to "reclaim" her life (Bizub 2013). Alternatively, in the words of Henderson (2004), traveling from being paralyzed by depression, emotional turmoil, poor memory and concentration, and sleeplessness to being gainfully employed and having meaningful relationships where she was "thriving not just surviving" and accepting her diagnosis and need for medication as important elements of her eventual recovery.

Some patients have seen newer psychotropic medications as being the foundation for recovery, along with support, rehabilitation, training, and acceptance (Paquette and Navarro 2005), or simply that medications meant "not being sick" (O'Neal 1984). In a study describing patient's perceptions and experiences while being treated with long-acting depot antipsychotics, Svedberg et al. (2003) described individuals reporting the state of psychosis as having been "lost in an

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estranged world" and where they felt "anguish and insecurity." Moreover, these periods of psychosis actually interfered with aspects of life that were key to recovery, such as work, education, family interactions, parenting, and financial independence. They were motivated by distressing memories of episodes where they had been off medication with subsequent relapse and loss of control. They understood the medications as being a prerequisite for maintenance of health and functioning, and attributed regaining "hope" to the medications. Side effects were described as a "necessary evil" to obtain this (Svedberg et al. 2003).

Often hospital settings are the first exposure people have to adjust with the mental health system early in the course of severe mental illness, and this experience can affect their attitudes toward the treatment that are offered for years, if not life. Psychotropic medications are frequently a large part of the armamentarium offered during this stage. In a qualitative study of subjective experiences of illness recovery in persons treated for first episode psychosis several themes were noted, including symptom recovery, reconciliation of the meaning of the illness, regaining control, and finally negotiation and acceptance of treatment including medications (Windell et al. 2012, 2015). Symptom resolution was identified as an important "turning point" in the beginning process of obtaining recovery, and "finding the right medication" was a significant element of this. In this study, it was also found that medications had other meanings that affected a person's outcome, including acceptance they were "ill" which led to initial nonadherence. This illustrated that there is a process that persons go through before they fully accepted their illness, and the idea of the need for external sources of stability may not have been automatic. Specifically, persons spoke of the difficulties involved in the process of accepting the need for medications, especially when the medications were not initially effective in treating symptoms, or when side effects interfered with other "valued states" such as alertness or activities that required cognitive performance. For some, medications were seen as an integral part of recovery because of the associated symptom reduction attributed to medications, but others saw the need to take medications as a barrier because it implied that the illness may return and was a chronic condition.

Deegan and Drake (2006) stipulated that "choice, self-determination, and empowerment" are foundational values for persons with disabilities, and many view recommended treatments as worse than the condition. They also pointed out that the research from which our medication treatment algorithms are derived is usually based on population averages, not individuals and their "unique concerns, values, and life context." Medications can be seen as unnecessary, ineffective, or an interference with the process of recovery. Persons may feel that they lose who they are with the effects of medications. One way to reframe this issue is the "illness" versus "wellness" model. In the first, the person has a diagnosis with associated symptoms, the doctor prescribes medications to treat these symptoms, and either the illness is cured or managed chronically. The second entails the person's aspiration for a meaningful life including hope, empowerment, self-determination, relationships, and employment. These viewpoints are not mutually exclusive. Medications can be an important tool for many in taking the first steps in obtaining eventual recovery. The mistake the clinician can make is to assume that cessation of auditory hallucinations, or depression, or other debilitating symptoms is the desired ultimate result of treatment, thinking that a pill will instill "hope and empowerment." Actually, a pill may cause adverse effects that the person finds worse than the symptoms, or the person may feel like they will be irrevocably changed by the medication, and not be "his self" any longer (Piat et al. 2009).

Medications are just one tool that is available to persons with mental illness to be utilized in a collaborative fashion with a clinician's guidance. With a view of the human continuum as encompassing suffering, loss, and grief as well as joy, accomplishment, and purpose, interventions provided by the medical-model, specifically medications, are not enough in helping people

discover their own paths to recovery. Some postulate that physicians are only treating superficial behavioral manifestations of the complicated internal processes that lead to mental illness. An individual can feel that administering medications may actually alter his thought processes and emotions, leaving him with a sense of loss that is greater than the illness itself. The interventions proposed by the recovery model can fill the void left by the "extinction" of these symptoms. As stated by Lunt (2002), "in the views of many people with mental illnesses, the biochemical solution alone will only propel one partially down the road to recovery."

## Emergency Involuntary Care

When discussing recovery-oriented pharmacotherapy in inpatient settings, it is impossible to avoid the issue of forced psychotropic medications. The primary psychiatric diagnoses that prevail in inpatient settings include Schizophrenia, Bipolar Disorders, and Major Depressive Disorders (Watanabe-Galloway and Zhang 2007) and these conditions often affect cognition and thought processes needed to make rational decisions about care during times of crisis and decompensation (Austin et al. 2001; Martinez-Aran et al. 2004; O'Leary et al. 2000). By default, clinicians may resort to paternal medical decision-making when the person is impaired. There can be conflict when a person, or his caregivers, do not agree with the clinician's recommendations, regardless that they originate from current evidence-based treatment algorithms.

Frese et al. (2001) discussed a person's ability to accept or reject evidence-based care, and suggested that more disabled persons may need the more paternalistic medical model until they have progressed to the point where they are capable of making their own decisions. They and other authors have also suggested that regardless of a person's functioning, the instillation of hope, responsibility, and internal control is necessary at all stages of treatment (Bellack 2006; Fisher and Ahern 2002; Frese et al. 2001). Many authors support the notion that when individuals lack decision-making capacity due to the severity of his or her symptoms, other means must be utilized such as processes for involuntary treatment or preferably psychiatric advanced directives (Davidson et al. 2006; Drake et al. 2010), but the question arises on how to ensure that at least a foundation for recovery-oriented principles is developed and respected during this crucial period?

## Informed Consent

With the advent, in the late 1970s, of the legal concept of the right of psychiatric patients to refuse treatment, including psychotropic medications, different jurisdictions have developed varying approaches in adopting the *treatment* versus *rights* model of care. Depending on which side of this argument a particular jurisdiction has adopted, processes for involuntary treatment can be instituted with dominance of clinical versus judicial decision makers (Appelbaum 1988; Menninger 2001). See Table 7.1 for an outline of the requirements for *Informed Consent*.

Other authors have suggested a "sliding scale" for determining capacity as related to the dangerousness of the condition being treated versus

**Table 7.1** Requirements for informed consent

| According to legal standards for the informed consent process, one must have the ability to: |
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| 1. Express a choice |
| 2. Understand information relevant to the decision about treatment |
| 3. Appreciate the significance, for one's own situation, of the information disclosed about the illness and possible treatments |
| 4. Manipulate information rationally (or reason about it) in a manner that allows one to make comparisons and weigh outcomes |

Adapted from Wirshing et al. (1998)

the treatment provided. An example would be initiating low risk intervention known to improve outcomes versus an invasive, high-risk, non-proven procedure for the same condition. The first would only require assent, where the second would require a higher level assessment of decision-making capacity (Drane 1984). The presumption for some is that persons suffering from major mental illness cannot, by definition, participate in the informed consent process. In one retrospective study examining people with schizophrenia who participated in research protocols, it was determined that this was not the case. Taking the selection bias into account, (persons who were too ill to give consent were not included) the authors found that through the implementation of systematic and thorough informed consent procedures, including repetition and education about risks and benefits, that a large portion of study subjects were able to comprehend and retain all the critical components necessary for informed consent. They did find that "conceptual disorganization" was correlated with poor performance on informed consent procedures, but that psychosis per se did not interfere with comprehension and retention (Wirshing et al. 1998).

Many proponents of the recovery process do not see this aspect as an absolute issue. There are times when individuals cannot make decisions for themselves, and safety concerns are predominant. This can be seen as carrying the concepts of recovery further, as it emphasizes not just the rights of an individual to make decisions about his care, but his responsibility to the community he lives into not pose a danger to himself or others (Davidson et al. 2006). Also, taking personal responsibility for health and wellness, and one's own illness management, including acceptance of psychotropic medication when needed, can be seen as important components of obtaining recovery.

During times when involuntary treatment is necessary, recovery-oriented approaches are most critical, otherwise, "the treatment relationship is likely to disintegrate into a policing relationship that discourages the client's growth, development of new skills and acceptance of illness" (Noordsy et al. 2002). Deegan (2007) pointed out that most treatment algorithms do not make allowances for shared-decision making. There is literature that supports the fact that many persons with severe mental illness do have the capacity to understand their illness and treatment choices, and are capable about making rationale decisions. For those with temporary incapacity in emergency situations, Psychiatric Advanced Directives are a viable option consistent with recovery-oriented principles (Deegan and Drake 2006; Drake et al. 2010; Sowers and Quality Management Committee of the American Association of Community Psychiatrists 2005).

## Psychiatric Advanced Directives

This intervention was inspired by initiatives around patients' rights of self-determination at end-of-life that began in the early 1990s, and subsequently laws have been enacted in large percentage of jurisdictions in the United States and several western countries. There is as well a great deal of advocacy support for this concept with the hope of respecting individual's wishes during times of incapacitation due to decompensation. There are several alternative terms that are in use that refer to documenting these wishes including: advanced crisis planning, anticipatory psychiatric planning, joint crisis planning, and "Ulysses directive."

The two primary forms of psychiatric advanced directives focus on treatment decisions where the person outlines what treatments are preferred and what is not acceptable, versus identification of who will be a proxy decision maker during times of incapacitation. Proposed advantages of this approach encompass enhanced autonomy, reduced familial conflict over treatment decisions, clinician acceptance of patient self-determination, and decreased service use, e.g., hospital admissions, length of stay, involuntary commitment, and interaction with law enforcement.

Despite the widespread support and enactment of these types of directives, the penetrance into common use has fallen short. There are of course

some real barriers to appropriate implementation, such as concerns over the person's capacity to enact this type of legal document (the same issues that would occur with end-of-life advanced directives, health-care powers-of-attorney, wills, and other binding contracts); clinician willingness to follow directives; the liability associated with following or not following directives; directives that contradict actual current treatment guidelines; and availability of the documents during times of crisis, i.e., midnight in the emergency room. This of course is not an all-inclusive list, but does illustrate there are valid barriers that have to be addressed (Campbell and Kisely 2009; Nicaise et al. 2013). One very important issue is the reality that most people will not have the foresight to create this type of document before they have their first episode of severe psychiatric illness.

Several groups have examined outcomes related to implementation of these types of directives, since their advent. In the strict methods of the Cochrane Review, no improvement was found in general outcomes such as voluntary and involuntary admissions, hospital length of stay, interaction with law enforcement, or outpatient contact. In their review, they did not find data on social functioning, imprisonment, quality of life, self-esteem, accommodation status, or career/family satisfaction, all purportedly important factors in recovery. They did mention one non-randomized study that demonstrated improvement in working relationships with clinicians and satisfaction with mental health treatment on short-term follow up. They also suggested that more intense methods such as joint crisis planning might have some positive effect on reducing involuntary admissions (Campbell and Kisely 2009). In another systematic review of research related to this topic, Nicaise et al. (2013) identified three frameworks for expected benefits of psychiatric advanced directives: (1) enhancement of the user's autonomy, (2) improvement of the therapeutic alliance, and (3) integration of care through health providers working in partnership. They also demonstrated that these benefits have not been adequately assessed, but rather the focus has been on organizational outcomes.

The *American Association of Community Psychiatrists Guidelines for Recovery-Oriented Services* stipulated that there will be crisis management and hospital diversion plans with "participatory" psychiatric medication management. Providing information for informed decisions when persons are capable of participating is seen as critical. In these recommendations, coercive treatment is not considered compatible with recovery-oriented care. Though it is acknowledged that at times this is necessary, the time should be kept to a minimum, and voluntary care instituted as soon as possible. Moreover, even during times of involuntary care, compassion and respect are tantamount (Sowers and Quality Management Committee of the American Association of Community Psychiatrists 2005).

## Stabilization Versus Recovery: Phased-Linked Treatment

There is a body of literature that reports the occurrence of recovery in people with schizophrenia who were not maintained on antipsychotics, though most research does indicate better outcomes with early aggressive identification and treatment of psychosis, and subsequent maintenance on antipsychotic medication (Bellack 2006). Psychotropic medications have been shown to reduce debilitating symptoms and risk of relapse in both bipolar disorder and severe recurrent and major depressive illness as well (Geddes et al. 2003; Kaymaz et al. 2008; Moller and Nasrallah 2003; Sachs and Rush 2003). Some authors see the installation of hope in periods of greatest instability as crucial to eventual recovery. In keeping with this viewpoint, the *how* is as important as the *what* with regard to treatment delivered. Even during instability is the individual encouraged to participate and take personal responsibility? Does the clinician instill hope instead of paternalistic blame? Evidence-based practices are not incompatible with recovery, but ideally implemented in partnership (Bellack 2006).

From the perspective of a psychopharmacologist, the clinician establishes symptom clusters

that indicate diagnosis, and therefore suspected etiology of illness. Current methods of research focus on reduction or elimination of these symptoms, while ideally avoiding unbearable and/or dangerous side effects. The focus of rehabilitation is strengths driven toward the goal of improving functioning in aspects of the illness that are not amenable to chemical interventions. Psychopharmacology can be conceptualized as a stepping-stone that supports re-attainment of healthy functioning. Specific examples given are the improvement in functioning that occurs with treatment of positive symptoms (delusions, hallucinations, paranoia, disorganized thinking), while not worsening debilitating side effects such as extrapyramidal symptoms or cognitive dysfunction.

With direct reference to schizophrenia, several symptom clusters are countered to obtaining recovery. Positive symptoms are inversely correlated with "life-satisfaction," and are associated with dangerous behaviors that can lead to hospitalization. Negative symptoms are thought to be strongly associated with functional disability and poor self-care, and interfere with independent living skills, vocational status, and quality of life. The practice of psychopharmacology can enhance, or at least not impede promotion of hopefulness, personal responsibility, self-control, and life "beyond illness" (Noordsy et al. 2000; Tandon et al. 2006).

In his book, *Recovery From Disability: Manual of Psychiatric Rehabilitation,* Liberman (2008, pp. 101–103) presented the concept of phase-linked treatment, which involves periods of prodromal illness, periods of acute symptoms and potential associated crisis, the period of stabilization, and then subsequent stability where the person hopefully progresses to full recovery. These are not seen as static phases that occur in linear fashion, but individual paths where people may fluctuate between various aspects of illness and recovery. When traversing these phases, movement is not a regimented and lock step, but rather a dynamic, individual process.

By definition, persons newly admitted to the hospital would qualify as being in the acute or stabilization phase which precludes taking the next steps to full recovery until resolved (an exception may be long-term forensic units where the individual is still hospitalized for legal reasons, not psychiatric instability). As the person moves from the acute phase through the different stages, symptoms will become less prominent and debilitating, and the person will regain psychosocial functioning. During the acute and stabilization phases, symptoms are at their peak or starting to resolve. Cognitive abilities and resilience are limited. Interventions must be adjusted to avoid over taxation of the person's capacities and possible exacerbation of symptoms. The treatment team will have to take a more direct responsibility in interventions to encourage adherence, though this does not preclude collaborative approaches. During the stable phase, the individual can tolerate more intensive, evidence-based rehabilitation that can be personalized to improve vocational and social functioning.

From a pharmacological viewpoint, the highest priority during the acute and stabilization phases is to control and alleviate symptoms and associated problematic behaviors. This requires appropriate diagnosis of the condition with identification of predominant symptoms (i.e. psychosis, mania, depression) and provision of optimal diagnostic-specific psychopharmacological interventions, if indicated. Throughout all of these phases, collaboration between the care recipient and clinicians is necessary and marked by mutual respect, shared decision-making principles, and engagement in treatment adherence for pharmacological and non-pharmacological interventions. The focus during the acute and stabilization phases is on reducing symptoms and minimizing side effects, to move the person past dangerous behavior, and begin reintegration into the community so that the process of full recovery can begin (Liberman 2008; Tandon et al. 2006).

## Recommendations for Initial Medication Choices

Tandon et al. (2006) focused on the management of schizophrenia, but their approach in maximizing effectiveness of treatment is generalizable

to other conditions. This involves ongoing monitoring and management of four outcome domains: symptom of disease, disease burden, treatment burden, and overall health and wellness. Symptoms of disease involve positive and negative symptoms, aggressiveness, hostility, mood dysfunction, and cognitive dysfunction. This could include manic and depressive symptoms associated with other serious mental conditions as well. Treatment burden includes side effects such as extrapyramidal symptoms, metabolic issues, sexual dysfunction, and other adverse effects resulting from psychotropic medications. Disease burden encompasses the impact on family, caregivers, social supports, healthcare cost, as well as vocational, interpersonal, and educational functioning. Last, overall health and wellness include social reintegration, independence, vocational/educational functioning, and physical health. In this model, psychopharmacology is seen as a component of the multiple psychosocial interventions that promote recovery (Tandon et al. 2006).

The first issue to address is "evidence-based care" being provided? Part of the impetus for quality improvement initiatives in mental health systems was the widespread evidence that many mental health systems were not following the prescribing guidelines, providing newer possibly more effective and less-toxic pharmacological agents, nor access to appropriate care, both in crisis and community settings. Part of this push came from regulatory and professional bodies, but several consumer advocacy groups have asked for access to newer treatments and adherence from their providers to prescribing guidelines (Drake et al. 2001; Kingsbury et al. 2001; Lehman and Steinwachs 1998; Torrey et al. 2001).

The second is to remember that though there is good research to support current recommendations for the pharmacological treatment of the major diagnostic categories of mental illness, these are based on statistical averages in large population groups, not individuals. Third, research directly linking pharmacotherapy to recovery is scant. At present, we examine domains which can be tied to elements that are associated with recovery, e.g., time to relapse, decrease in hospitalization rates, decrease in symptom clusters that cause distress and disability, improvement in elements of cognition (Liberman and Kopelowicz 2005). All important issues, but again are they directly linked to a person's ability to recover, with its subjective elements of hope, empowerment, self-direction, self-sufficiency? Another consideration is that laypersons may have different concepts of what "evidence-based" means, or may not even be aware of the methods behind formulation of treatment recommendations (Tanenbaum 2008; see Table 7.2).

In the *Roadmap* developed by Weiden et al. (2007), they discussed expansion of the maintenance model where the emphasis is placed on stabilization, maintenance of stability, and relapse prevention to include the next steps in the recovery model, where the individual obtains further gains in physical and emotional health. These two models, maintenance and recovery

**Table 7.2** Consumer perspectives on evidence-based care in public mental health

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| 1. Consumers want information, including but not limited to scientific information, about recommended treatments |
| 2. Though consumers take this information seriously they are focused on their individual experience as opposed to aggregate data collected in research protocols |
| 3. They are experts in their own illnesses |
| 4. Communication and discussion about treatment options with their psychiatrist is key, even if they do not agree |
| 5. Medications are only a small part of what they need and only give the person a "chance to learn and see." |

Adapted from Tanenbaum (2008)

oriented, are not seen as contradictory or in opposition, but rather logical extensions of each other. In times past, it was thought to be too risky to alter medication treatment regimens once stability was obtained. With inclusion of recovery concepts into the medical model, continued improvement in functional outcomes is expected.

Pharmacological management is one tool that actively facilitates continued recovery beyond initial stabilization and associated medication side effects. With the maintenance model, the goals would be achievement of stability, prevention of relapse, and worsening of symptoms (especially those associated with potential harm) and avoidance of adverse effects of treatment. These all are important objectives, but with recovery-oriented care continued efforts to improve health and wellbeing would also involve the reduction of overall burden of side effects, continued improvement from that obtained at initial stabilization, reduction in other functional impairments, and ultimately the lack of psychiatric symptoms and disease. Though addressing one of these can threaten or worsen another aspect, e.g., dose reduction to minimize side effects leading to recurrence of psychotic symptoms (and possibly destabilization). With these objectives in mind, detailed knowledge of psychopharmacology is needed to address efficacy for specific conditions, possible side effects in the context of treating an individual, general physical health issues that can be influenced by psychopharmacological agents, and interactions related to polypharmacy both for somatic and psychiatric medications.

There are multiple respected algorithms/guidelines from different organizations that cover recommended psychopharmacological treatment for the primary diagnoses of persons with severe mental illness. Examples of these guidelines include but are not limited to those for schizophrenia (Hasan et al. 2012; Moore et al. 2007), bipolar disorders (Sachs et al. 2000; Yatham et al. 2013), and severe major depressive disorders (American Psychiatric Association 2010; Bauer et al. 2013). These were developed by clinical and research experts in the field and are valuable in that they reduce the overwhelming, and sometimes conflicting, body of published research into digestible documents for clinicians (Mellman et al. 2001). They are based on a synthesis of drug trial data, which, for the most part, are based on large groups of people though, not individuals. Often these protocols severely limit variation in their subject matter (diagnosis, age, health status, co-morbidities, substance use, adherence), and hence may not be completely applicable to both the psychological and physical health needs of individuals. Therefore, both pharmacodynamic (what drugs do to the body, e.g. receptor binding) and pharmacokinetic (what the body does to the drug, e.g. half-life, metabolism, drug clearance) must be an integral part in making collaborative decisions with individuals regarding their care (Weiden et al. 2007).

## Individualization of Pharmacological Interventions: Efficacy Versus Side Effects

### Pharmacokinetic and Pharmacodynamic Interactions

There are several determinants of drug response/efficacy and the potential for adverse effects. The drug binds has an intrinsic effect on the site of action, e.g., a neuron receptor, ion channel, chemical transporters, or cell-associated enzymes (Stahl 2013, Chap. 2). In order for the drug to have an effect, it must reach the site of action in sufficient concentration. This is determined by how efficiently the body absorbs the drug, where the drug is distributed (i.e., determined by relative blood flow in different areas of the body, storage in fat cells, and protein binding), by what mechanism and rate the body metabolizes the substance (e.g. liver; and eventually how it is eliminated, e.g. urine, feces). There is biological variation, which can shift the usual dose response curve making the individual more or less sensitive to both clinical effectiveness and incidence of adverse reactions to a drug. These include, but are not limited to genetics,

age, co-occurring health problems, and the individual's internal environment (Weiden et al. 2007).

Several mechanisms are involved, including metabolic interactions that raise or lower plasma drug levels, clearance and excretion, distribution of the drug in the body, and either potentiation or competition at the primary site of action (e.g. neurotransmitter receptor). Pharmacokinetic interactions involve the effect the body has on the drug, which increases or decreases the concentration of drug available in the body. There are four primary phases involved in this, including absorption, distribution, metabolism, and excretion. With few exceptions, psychotropic drugs are lipophilic agents that are extensively metabolized in the liver. Most pharmacokinetic interactions occur at a metabolic level and usually involve changes in the activity of the liver cytochrome P450 system. The activity of this system is genetically determined and may be profoundly influenced by environmental factors such as concomitant administration of other drugs, primarily through enzyme inhibition or induction. Enzyme inhibition usually involves competition with another drug at the enzyme-binding site, while induction occurs when a drug stimulates the synthesis of more enzyme proteins. There are also pharmacodynamic interactions that alter the effect the drug has at its site of action. Two drugs can interact at the same or interrelated receptor sites, resulting in additive, synergistic, or antagonistic effects (Besag and Berry 2006; Spina et al. 2003).

Polypharmacy has become very common and often antipsychotics, antidepressants, and mood stabilizers are prescribed together, in addition to many medications prescribed for co-occurring somatic conditions. There are several reasons for polypharmacy, and some are justified such as combinations of different classes of agents for treatment of acute mania, treatment of persistent residual symptoms of depression, and refractory psychosis. Additional agents can be utilized to treat known side effects such as anticholinergics for antipsychotic-induced extrapyramidal symptoms. Sometimes there are co-occurring conditions, e.g., a person with schizophrenia and posttraumatic stress disorder, or bipolar disorder and HIV. A person may have multiple symptom clusters warranting different agents, such as a person with schizoaffective disorder needing a mood stabilizer and antipsychotic. There are several possible interactions between these medications plus any other prescribed, over-the-counter, or herbal agents people may be taking for other conditions. These interactions can have both positive and negative actions on efficacy.

Though not all of these interactions are clinically relevant, there is the chance of an increased risk for adverse effects that can affect quality of life, and even safety. Factors that have to be taken into account when evaluating clinical relevance of interactions are drug, patient, and epidemiological-related factors. Drug-related factors include concentration, therapeutic effect of substrate, extent of metabolism of substrate through affected enzyme, and presence of active or toxic metabolites. Patient-related factors include phenotype and genotype of the person involved, and special populations that are at increased risk, e.g., the elderly. Epidemiological factors basically involve whether there is a chance the drugs will be used concurrently, meaning are they both available to the population involved (Spina et al. 2003).

Almost all medications have dose response curves where efficacy increases with dosage to a certain point, then side effects, and eventually toxicity predominates (occurs at different rates and concentrations for different drugs). There are variations in these curves between individuals, and the factors described above can all influence them as well, so the dose for efficacy, side effects, and toxicity can change during treatment for an individual. These issues must also be taken into account when discontinuing or changing doses/types of psychotropic medication. If a drug has a narrow therapeutic index, it is more likely to be at subtherapeutic or toxic levels. For example, serotonin-specific-reuptake-inhibitors (SSRIs) have a wide therapeutic index. They have many reactions through either induction or inhibition of their metabolism, but these interactions are less likely to have clinical relevance related to their levels. They can cause adverse effects through the interference of metabolism of

other agents though. For example, fluoxetine inhibits the metabolism of haloperidol and fluphenazine, and therefore potentially raises the blood concentrations of these drugs, thereby increasing the risk for extrapyramidal symptoms. Second-generation antipsychotics are only weak inhibitors of CYP isoenzymes at therapeutic concentrations, and thus are less likely to interfere with the elimination of co-administered drugs. The administration of inhibitors or inducers of their metabolism can raise or lower their levels though, e.g., fluvoxamine can double olanzapine levels, ketoconazole can quadruple quetiapine levels, whereas phenytoin can reduce the quetiapine by 80 % (Spina et al. 2003).

Psychotropic drugs also make persistent changes in the neurotransmitter receptor profiles in the nervous system, which can become important when changing doses or medication regimens. An example is the withdrawal dyskinesia that can occur with antipsychotic induced upregulation of dopamine receptors and subsequent full or partial withdrawal of the blockade (Cerovecki et al. 2013), or anxiety induced by withdrawal of serotonergic antidepressants (Fava et al. 2015). If not explained to the person, this can have long-term effect on the person's willingness to adhere to future recommendations or other agents (as the new agent may be blamed). When medication changes do occur, the dosing and speed of a switch depends on possible withdrawal and rebound effects (Weiden et al. 2007). Discussed below are some of the variables that have to be taken into account when establishing psychiatric drug treatment regimens with care recipients.

**Gender**. Though there are gender-based metabolic differences regarding psychotherapeutic drugs, there are physiological differences that are more clinically relevant. There are differences in how men and women absorb, metabolize, and excrete a drug due to gastric motility, expression and activity of intestinal and liver enzymes, sex hormones (specifically estrogen), and protein binding. The main differences in how medications are absorbed and distributed are due primarily to factors such as differences in body mass index, body composition, plasma volume, organ blood flow, and the extent of tissue and plasma protein binding. Women generally have a higher body-fat percentage, decreased body weight, decreased plasma volume, and decreased organ blood flow as compared to men, leading to disparities in the rate and extent of drug distribution. Due to these factors, there is a potential for increased clinical effect or side effects with psychotropic medications (e.g. the potential for reduction in psychotic symptoms, but also increased extrapyramidal side effects with antipsychotics). Women generally need lower doses of antipsychotics than men, and there is some evidence that women are more prone to both the neurological (i.e. EPS and tardive dyskinesia) and metabolic effects of antipsychotics (Gandhi et al. 2004).

**Pregnancy**. Many women under the care of inpatient facilities are of reproductive age, or even sometimes pregnant during their psychiatric hospitalization. Even if a woman is not expectant, the potential for future childbirth is an important issue for many. There are several non-medication-related issues involved in pregnancy, including the potential adverse outcomes associated with untreated psychiatric illness due to possible direct physiological derangements, poor physical health of the mother, interference with child care in the postnatal period, and unfortunately sometimes harm committed by mother to the infant due to depression or psychosis. When counseling women on these issues, the potential effect of psychiatric medications on the fetus is unavoidable and must be taken into account when making treatment recommendations to such persons, including the possible congenital malformations associated with psychotropic medications when administered during the pregnancy. There are definite malformations associated with drugs such as valproate or carbamazepine. There are possibly serious issues with commonly prescribed antidepressants such as an elevated risk of miscarriage, preterm birth, decreased birth weight, and postnatal pulmonary hypertension. There are also outcomes associated with antidepressants such as increased incidence of low birth weight infants, preterm birth, or delivery complications (e.g. post-natal adaption syndrome). Medications may have strong effect on the mother such as increasing the risk of

gestational diabetes, obesity, metabolic syndrome, and hypertension all of which can increase the risk to the fetus. Finally, many psychotropic medications are excreted in the breast milk. These are all valid concerns, but none absolutely preclude administration of psychotropic medications in pregnancy and the postnatal period, if indicated. Many women will have concerns over ingesting psychiatric medications, and these concerns have to be respected and addressed with her and her partner, if present (De Hert et al. 2011a, b; Pearlstein 2013).

**Children and Adolescents**. It is beyond the scope of this chapter to cover treatment recommendations for children and adolescents. In addition, the question of choice and self-determination is less relevant because legally the parents are the ultimate decision makers in deciding what care their children will receive. Though parents can certainly be exposed to and educated about recovery-oriented concepts, and clinicians should utilize the same approaches, there is a different context for these discussions.

**The Elderly**. The primary concerns with the elderly are etiology of psychiatric symptoms and their increased susceptibility to medication adverse effects. As a general rule, the later the onset of symptoms (mood and psychosis) the more likely there is an underlying medical reason such as cerebral vascular disease, cancer, Parkinson's, Alzheimer's, and even arthritis, which must be ruled out first and much more aggressively than would be the case for a younger population (Krishnan et al. 2002). Furthermore, many psychiatric symptoms such as depression, anxiety, mild cognitive issues, and impulse control issues can be the hallmark of various types of dementia, and precede the full onset by months to even years. Aggressive identification and treatment of these conditions are crucial as often the conditions can be reversed or at least mitigated, providing the person with years more of fruitful and fulfilling life (Alexopoulos et al. 2002; Charney et al. 2003). Ideally, this should occur before the person starts losing decisional capacity.

Regarding medication side effects, the elderly heightened sensitivity is due to several factors. The elderly react differently to medications, exhibiting a different response to drugs as compared to younger persons and to adverse effects of these same medications. The elderly have less functional reserve, both mental and physical, which is a natural occurrence with the aging process. There are physiological changes that occur, which affect both metabolism and clearance of medications and also add to drug–drug interactions (Campanelli 2012). Particular side effects of concern are sedation, anticholinergic side effects, and postural instability caused by hypotension. Regarding the gastrointestinal system, they have decreased stomach acid, smaller absorptive surface, decreased intestinal motility, and possible delayed absorption due to more common use of antacids. The elderly have increased total body fat so fat-soluble medications are distributed and stored more extensively. They have lower serum albumin levels, affecting protein binding and hence increasing plasma concentration of the drug. Their livers do not function as well so they have decreased ability to metabolize drugs. Finally, their kidneys have decreased functional capacity so many drugs and their metabolites are not excreted as efficiently. Other issues that have to be considered with the elderly are their greater propensity for poor nutrition, co-morbid medical conditions, and concomitant medications that may interfere with the metabolism or therapeutic effect of a psychiatric medication (David 2010; Mangoni and Jackson 2004; Pollock et al. 2009).

**Co-morbid Medical Issues**. There is evidence of increased medical co-morbidity among people with mental illness, which can affect the person's sensitivity to psychopharmacological agents, the risk of side effects, and severe adverse events. Persons in this class have also been found to have a higher incidence of multiple co-morbidities, e.g., a person with schizophrenia, respiratory disease, hypertension, and diabetes (Dickey et al. 2002). People with severe mental illness (i.e., schizophrenia, bipolar disorder, and major depressive disorders) have 2–3 times the mortality and 13–30-year shorter life spans than the general population, largely attributed to medical co-morbidities. This increased risk is

multifactorial, including genetics, diet, smoking, level of exercise and physical activity, illness associated issues, and disparities in health care access and utilization. Specific diseases associated with increased risk in the context of severe mental illness include tuberculosis, HIV, Hepatitis B and C, obesity-related cancer, osteoporosis/decreased bone mineral density, poor dental status, impaired lung function, sexual dysfunction, and obstetric complications. There are also pre-existing issues with cardiovascular disease (CV) including myocardial infarction, cerebral vascular disease including stroke, and obesity-related metabolic disturbances of diabetes, dyslipidemia, and metabolic syndrome (De Hert et al. 2011a, b).

**Genetic Variation**. There has been a great deal of research and interest in genetic polymorphisms, or natural variations in genes, DNA sequences, or chromosomes that do not have adverse effects on an individual and occur with high frequency in populations. These variations are not necessarily an advantage or disadvantage (like blood types), but do increase overall variability of the species (U.S. National Library of Medicine 2015). Areas that are being studied include genes encoding metabolic enzymes, blood-brain barrier transport mechanisms, neurotransmitter receptor expression, and neurotransmitter storage and degradation. Of particular interest is relative responsiveness to medications and risk of adverse effects. There is evidence of these variations with regard to antipsychotics, antidepressants, and mood stabilizers (Brandl et al. 2014; Fabbri et al. 2014; Kato and Serretti 2010).

One example to elucidate this topic is the differences in the liver cytochrome system, where variability in genes that encode for this system affect enzyme activity, and subsequent metabolism of medications, including many psychotropics. Genes encoding for the CYP system are highly polymorphic with 80 variations known for one element the CYP2D6 alone, which is involved in the metabolism of many antipsychotics. There are differences in incidence of these genes within ethnic groups and between different cultural groups. Based on the combinations of these variations, people can be ultra-high, intermediate, or poor metabolizers, e.g., carriers of the allele that is defective for CYP2D6 function can have up to 80 % higher plasma levels of risperidone (a commonly used second generation antipsychotic). Though there are no strong data that supports differential treatment responses to antipsychotics based on this particular variation, there is good evidence of its effect on the incidence of adverse events, particularly antipsychotic-induced weight gain, tardive dyskinesia, and extrapyramidal symptoms (Brandl et al. 2014). Though testing for these differences has not reached mainstream clinical utility yet, the science behind this will definitely affect how psychiatric drugs are developed, and consequently prescribed in the future (Malhotra et al. 2004).

## Medication Side Effects

As described above, there are many variables that affect both effectiveness and the incidence of adverse medication effects. When looking at several measures associated with domains of recovery, fewer medication side effects (among other measures) were associated with general life satisfaction, hope, and empowerment (Resnick et al. 2004). The person's internal experience with medications needs to be addressed, as some adverse effects may not be well elucidated in tables derived from safety and tolerability trials. Just as with efficacy measures, information gathered on medication side effects is based on large population groups included in research. Often inclusion criteria for safety and efficacy protocols are severely restricted and do not reflect the diversity of co-morbidities, age, and health status of the general population.

Safety and tolerability profiles differ across individuals, and psychopharmacological plans should be customized to reflect the needs of an individual. Individuals have described the effects of medications as "strange and threatening," especially because the people involved did not know that the medications were causing these experiences. Other complaints included feelings

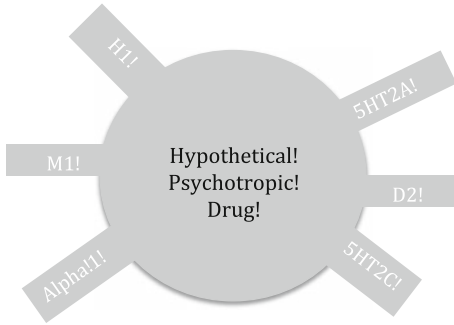


**Fig. 7.1** Hypothetical psychotropic drug illustrating receptor site of action associated with potential clinical efficiency and or side effects

of tiredness, dullness, feeling like a "zombie," and being cut off from life and creativity. Some felt this was worse than psychosis (Svedberg et al. 2003). Absence of side effects is not realistic, but there is a balance of symptom reduction versus medication side effects that should be taken into account in a collaborative fashion with an individual when making treatment decisions. This also applies to the emergence of adverse outcomes later in the course of treatment (Tandon et al. 2006). See Fig. 7.1 and Table 7.3 for an example of the complex interplay between psychotropic drug interaction with neurotransmitter receptors and subsequent efficacy and/or side effects.

The recent update of the World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for treatment of schizophrenia (Hasan et al. 2013) stated that the main goals of the stabilization phase in the treatment of schizophrenia are to facilitate continued symptom reduction, consolidate remission, and promote the process of recovery. They continued with the following stipulations for the first few months post hospitalization: ongoing symptom remission must be ensured; there should be maintenance or improvement in the person's level of functioning and quality of life; that there is continued monitoring for adverse treatment effects; and steps are taken to ensure relapse prevention. In these guidelines, they stated that psychopharmacologic management must be individually tailored to the needs and preferences of the person, focusing on relapse prevention, symptom suppression, and improvement in subjective wellbeing and quality of life. Based on their review of the literature, they stated that continued treatment with adequate dosing of antipsychotic medication would reduce the risk of relapse after a psychotic episode. They also stated that medications that were effective in eliminating or reducing psychotic symptoms in the acute phase should be continued for at least six months post discharge (Hasan et al. 2013).

The purpose in outlining these recommendations is to emphasize the importance of medication adherence after a person has been hospitalized, to help ensure ongoing stability so the individual can continue on his or her path to full recovery. Relapse of symptoms, decompensation, and rehospitalization all are barriers to this goal. One of the most often cited reasons for medication discontinuation, or expression of choice, in persons with serious mental illness is side effects. No matter the stage of stabilization versus recovery a person is in, the clinician needs to take this into account when developing a pharmacotherapy plan. Side effects have several realms, including the initial discomfort (sometimes actually expected with many psychotropic medications), long-term health concerns (metabolic issues, tardive dyskinesia), and stigma associated with being on psychotropic medications (Tandon et al. 2006).

In one recent large study based on interviews of 876 persons identified as having schizophrenia that were prescribed antipsychotic medication, it was determined that side effects were prevalent at about 86.19 % (Dibonaventura et al. 2012). In addition, 42.5 % of this group acknowledged at least partial nonadherence with psychotropic medications. The categories of side effects that were found to be significantly associated with nonadherence were extrapyramidal symptoms, sedation, prolactin/endocrine derangements, and metabolic disturbances. They also found that this nonadherence was associated with an increased frequency of emergency room visits, hospitalizations, and healthcare resource utilization.

It is necessary to assess side effects that have been present in the acute phase and to adjust pharmacotherapy accordingly in order to

**Table 7.3** Examples of neurotransmitter-associated potential positive clinical effect versus adverse side effects (not all-inclusive)

| Neurotransmitter receptors affected by psychotropics | Potential positive clinical effect | Potential adverse side effect |
|---|---|---|
| *Dopamine* | | |
| D2 | Antagonism reduces psychotic symptoms | Antagonism leads to: Prolactin elevation-amenorrhea, galactorrhea in women; gynecomastia in men; sexual dysfunction in both sexes<br>Parkinsonian symptoms (EPS)-dystonias, tremors, bradykinesia<br>Long-term blockade thought to lead to Tardive Dyskinesia<br>Antagonism can possibly aggravate cognitive issues in Schizophrenia<br>Blockade can possibly aggravate apathy, anhedonia, decreased motivation, loss of interest, and joy from social interactions |
| *Serotonin* | | |
| 5HT2A | Antagonism reduces EPS, prolactin elevation<br>Antagonism possibly reduces depressive symptoms<br>Antagonism may result in an increase in cortical dopamine improving cognition | Sexual dysfunction<br>Antagonism can lead to over activation with increased agitation, anxiety, and insomnia<br>Agonism can cause EPS symptoms |
| 5HT2C | Antagonism increases dopamine and norepinephrine in certain areas of the brain and possibly reduces depressive symptoms and improves cognition | Antagonism thought to lead to weight gain<br>Antagonism can lead to over activation with increased agitation, anxiety, and insomnia |
| *Acetylcholine* | | |
| M1 | Antagonism can ameliorate parkinsonian symptoms | Antagonism leads to: Sedation and deficits in memory and cognition<br>Anticholinergic effects:<br>Dry mouth, Constipation,<br>Tachycardia, Blurred vision<br>Urinary retention |
| *Histamine* | | |
| H1 | | Antagonism leads to:<br>Sedation<br>Increased hunger<br>Weight gain<br>Postural dizziness |
| *Alpha-adrenergic* | | |
| Alpha 1 | | Antagonism leads to: Orthostatic Hypotension<br>Dizziness<br>Tachycardia<br>Sedation<br>Priapism |

Derived from Ferguson (2001), Newcomer et al. (2013), Stahl (2013), Stahl et al. (2013)

minimize adverse outcomes. The relative benefits of the drugs versus their associated risk profiles, in conjunction with the person's personal experience, have to be taken into account when discussing treatment options with an individual. Quality of life is rarely a primary outcome measure in clinical trials. Therefore, it is usually not powered to detect differences between drugs (i.e. drug A has been shown to significantly increase quality of life over drug B). Citing the CATIE and Cutlass trials, Hasan et al. (2013) stated there was no difference between individual antipsychotics and between first- and second-generation antipsychotics in improving employment outcomes, participation in psychosocial rehab, quality of life, and quality adjusted life years, although there was a hint that there may be an increased subjective wellbeing with second-generation antipsychotics. However, they found that antipsychotic-induced side effects negatively influenced quality of life.

The primary groupings of antipsychotic-induced side effects, or as Nasrallah et al. (2005) termed "treatment burden," include extrapyramidal symptoms involving parkinsonian-like symptoms, such as muscle rigidity or tremors; metabolic issues including weight gain, diabetes, lipid abnormalities; anticholinergic side effects including blurry vision, dry mouth, constipation; elevation of prolactin which can lead to amenorrhea, galactorrhea, gynecomastia, decreased libido, and erectile dysfunction. All of these issues can possibly lead to secondary sequelae that can be as debilitating as the primary side effect, e.g., antipsychotic-induced obesity leading to sleep apnea, insomnia, and hypertension. Antipsychotic associated side effects of EPS, sexual dysfunction, and psychological experiences as described above are associated with a decreased sense of wellbeing with related negative influence on medication adherence (Fenton et al. 1997; Karow et al. 2007).

**Extrapyramidal Symptoms (EPS) and Tardive Dyskinesia (TD)**. In registration trials and other studies, EPS is one of the largest offenders cited for drug discontinuation. First-Generation Antipsychotics (FGAs) are known in general to have a higher incidence of extrapyramidal symptoms and tardive dyskinesia thought to be due to their differential effect on certain dopaminergic pathways in the brain involved in movement. There are also differential effects between the newer agents with some having a greater propensity for these conditions than others, again mostly due to relative differences in dopamine blockade. The primary treatments for EPS are anticholinergics, which are known to worsen cognition, one of the most debilitating symptoms of schizophrenia and other conditions, plus other side effects associated with anticholinergics themselves, such as dry mouth, constipation, blurred vision. Avoidance of these conditions is at least possible and certainly should be part of the discussion with people receiving these types of medications (Minzenberg et al. 2004; Nasrallah et al. 2005; Weiden et al. 2007).

**Weight and Cardiometabolic risk**. Persons with schizophrenia and other major mental illness have been shown to die younger primarily from CV and are more prone to risk factors associated with CV disease, including obesity, diabetes, smoking, dyslipidemias, and hypertension. Psychotropic medications, with particular concern over newer antipsychotic agents but mood stabilizers and antidepressants as well, are known to be associated with several of these risk factors and can possibly exacerbate them (Weiden et al. 2007).

**Obesity**. Obesity increases the risk for diabetes, hypertension, cardiovascular disease, dyslipidemias, respiratory difficulty, reproductive hormone difficulties, and certain cancers that have an association with obesity, e.g., colon. Persons with severe mental illness are at increased risk for obesity, and this increased risk occurs before progression of their illness and initiation of psychotropic drug use. There are disease-specific risk levels, with schizophrenia (2.8–3.5× risk) > bipolar disorders > major depression. As mentioned previously, this is multifactorial, including lifestyle, illness specific, and medication side effect-related issues. Lifestyle refers to the association of these conditions with decreased physical activity and poor diet in general. Illness-specific issues include negative symptoms, disorganization of thought and behavior, and depression itself

all leading to reduced physical activity and poor self-care.

Antipsychotics, antidepressants, and mood stabilizers are all associated with sedation and its associated sequelae, but also they may directly cause or worsen obesity. Antipsychotics have been identified as the worst culprit, associated with weight gain in 15–72 % of persons receiving them. There is a differential effect among antipsychotics with some posing a greater risk than others, clozapine and olanzapine having the greatest risk, quetiapine and risperidone intermediate risk, and aripiprazole, asenapine, amisulpride, and ziprasidone having little effect. For the most part, FGAs have less risk, but have a stronger association with motor adverse effects. No antipsychotic should be considered to be totally weight neutral though.

**Metabolic Syndrome**. A grouping of conditions, including central obesity, hypertension, hypercholesterolemia, elevated triglycerides, and glucose intolerance or insulin resistance (incudes diabetes). Persons with metabolic syndrome have a five to sixfold elevated risk of developing diabetes, and three to sixfold increased mortality from coronary artery disease. Despite this well-known risk, and position statements from the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity, screening by primary care physicians and psychiatrists is inadequate for these conditions (Clark 2004).

**Diabetes**. There are several modifiable risk factors for the development of diabetes, including obesity, lack of physical activity, diets low in whole grains and vegetables, and smoking. People with schizophrenia, schizoaffective disorder, and bipolar disorder have 2–3 times increased risk for the development of diabetes. The risk for persons with severe depression is lower, but still increased as compared to the general population. Antipsychotics are associated with this increased risk with the same pattern as seen for weight gain.

**Cardiovascular disease**. Cardiovascular disease is one of the leading causes of death for people with major depressive disorder, schizophrenia, and bipolar disorder. The risk for bipolar disorder and schizophrenia is 2–3 times higher. Depression is an independent risk factor associated with morbidity and mortality from cardiovascular disease. The main factor linking depression and poor outcomes from cardiovascular disease is lack of physical activity. Depression also increases the risk of myocardial infarction 2.5 times in persons who have coronary artery disease. Here is an illustrative case example.

> Mr. B. was a 38-year-old male with a history of Schizophrenia who already had several of these risk factors, which if not dealt with would lead to long-term physical disability and possibly mortality at a relatively early age. He started suffering from a severe mental illness during his college years and had only obtained stability, and subsequent recovery, on olanzapine, an agent strongly associated with weight gain. His weight had increased by 30 lb since the start of treatment, but when discussing this issue he said that under no circumstances did he want to go back to the time when he suffered from distressing psychotic episodes and frequent hospitalizations. He was concerned about his weight and diabetes though because his dad died at 55 from a myocardial infarction. He has a wife, a job, and two young children and did not want to put them through this. Would it be recovery oriented to tell this man he has to come off this medication because of his other health problems, or to tell him he can't because of the possible decompensation that may occur?

**Cerebral vascular attacks**. Again associated with all the issues mentioned above, but there is an increased risk ranging from 1.3–3.3 times in persons with severe mental illness. Besides the association of antipsychotics with weight gain and obesity, there is a direct association with increased risk of cerebral vascular attacks.

**Elevated prolactin**. Due to the dopamine D2 receptor blockade caused by many antipsychotic medications, there is a risk of elevated prolactin levels (a hormone involved in regulation of the reproductive endocrine system), which can have serious and uncomfortable side effects in both men and women. In women, this can lead to menstrual disturbances, cessation of menses, and abnormal lactation. In men, this can result in gynecomastia or development of breast tissue, decreased libido, impotence, and ejaculatory dysfunction. There is a differential risk for this side effect as follows:

haldol > risperidone > ziprasidone > olanzapine > aripiprazole > clozapine > quetiapine.

Though not part of normal screening, prolactin levels can certainly be drawn in persons complaining of symptoms consistent with elevated levels, and other medication options that are not associated with this issue can be discussed (Weiden et al. 2007). Here is an illustrative case example.

> Ms. M. was a 35-year-old African American lady with a diagnosis of schizoaffective disorder who had been a long-term resident of a state operated psychiatric facility. When decompensated, she exhibited symptoms of paranoia regarding people stealing her possessions and trying to poison her, which had resulted in violence directed toward family, neighbors, and care givers in residential settings. In addition, she would have periods of "mania" where she would become sexually promiscuous and proposition strangers in her neighborhood. Other periodic problem behaviors included walking out in traffic and not attending to her physical conditions, which included obesity, diabetes, and hypertension. One persisting symptom was her delusional belief that she was pregnant, despite being provided with repeated laboratory results that showed she was in fact, not pregnant.
>
> For these conditions, she was prescribed divalproex sodium, oral haloperidol, and long-acting injectable risperidone. As long as she adhered to her medications most of these symptoms were controlled, but she often refused her medications, which had repeatedly led to residential placement failures and periods of instability in the hospital. This was the main barrier to her reintegration into the community. Her treatment team was frustrated by this, and during many discussions, she reported her reason for her medication refusal was her concern she may harm her baby as she was pregnant. Her psychiatrist at the time did have a good relationship with her, but was often stretched due to census, staffing, and acuity issues at the hospital. One day, things were calm, and two standing administrative meetings were canceled, so he decided to sit down with Ms. M and convince her that she was indeed not pregnant and therefore should be happy to take the medications he had prescribed. She was shown multiple recent pregnancy tests and a recent Ob-Gyn checkup that proved she was not carrying a fetus. She responded that the information provided was not accurate because she knew she was pregnant since her breasts were engorged and she occasionally lactated. The proverbial light bulb went off for the psychiatrist and he ordered a prolactin level, which came back at 165 ng/ml (normal for non-pregnant females < 25 ng/ml). He explained these results to Ms. M., which she accepted, and together they came up with a new pharmacological treatment regimen involving medications that were less likely to cause this adverse effect. With this change, her side effects subsided, her adherence improved dramatically, and she was successfully transitioned to the community three months later.

**Osteoporosis**. The three diagnostic groupings associated with severe mental illness are all associated with decreased bone mineral density. Again, this is multifactorial with smoking, reduced physical activity, alcohol abuse, vitamin D and calcium deficiency, and polydipsia. Antidepressants, particularly SSRIs are associated with worsening this condition and consequently an increased risk of fractures in the elderly (De Hert et al. 2011a, b).

**Oral health**. In general, people with severe mental illness have poor dental health. Besides many of the multifactorial issues mentioned above, including poor self-care, antipsychotics, antidepressants, and mood stabilizers are associated with xerostomia, or decreased salivary flow. This adversely affects the oral environment aggravating caries, gingivitis, and periodontal disease (De Hert et al. 2011a, b).

**Constipation**. Medication-induced constipation is common, but often under recognized and has not been a focus of research. In addition to the discomfort this can cause, there are severe sequelae associated with this condition, including paralytic ileus, bowel occlusion, and death. Active screening, monitoring, and treatment are recommended (De Hert et al. 2011a, b; Ozbilen and Adams 2009).

## Medication Adherence and Transition to the Community

Inpatient settings are an artificial environment that will not be sustained upon a person's discharge. Environmental stressors that may have contributed to the need for hospitalization have been temporarily suspended, but may return in full force. Schedules are controlled with definite "pill calls" and staff who diligently remind the

person to take their prescribed treatments. Medication side effects can be addressed immediately, and for the most part illicit substances and alcohols are not available. Upon discharge, the person typically has more control over management of the medications and individual barriers to ongoing adherence need to be identified and addressed as part of the discharge process.

Issues around medication adherence are complex. It would be nice if we simply could institute psychoeducational groups during the hospital stay and say that we have positively affected care recipient's adherence rates, but the research support for these assertions are equivocal (Barkhof et al. 2012; Zygmunt et al. 2002). In addition, there are many types of people who require psychiatric hospitalization, all of whom have different risk factors and who may require individualized approaches to improving medication adherence. Some issues that may arise, which adversely affect adherence, are the care recipient's insight into the illness and symptoms, active symptoms that may interfere with the cognitive aspects of health behavior, medication side effects, therapeutic alliance, environmental supports, and ongoing substance abuse.

Concerning people with schizophrenia receiving antipsychotic treatment, methodological factors cause large variation in adherence rates, ranging from estimates of 10–80 %, though this averages out to about a 50 % nonadherence rate. There are individual, medication, and environment-related reasons for this nonadherence and modifiable factors which should be targeted. In one study, Dolder et al. (2003) found that education alone was not adequate in changing adherence rates. They found that more intense interventions using behavioral and "affective" techniques in addition to education were effective in improving adherence. Education can be in verbal or written formats with a knowledge-based emphasis designed to convey information, e.g., one-on-one or group teaching with educational materials providing information about the purpose and potential side effects of medications. Behavioral interventions involve targeting or reinforcing specific behavioral patterns, e.g., skill-building practice activities, behavioral modeling, contracting, medication packaging, and dosage modification. This includes interventions such as simplifying regimens, teaching skills, and external cues such as medication reminder devices. "Affective" interventions influence medication adherence through appeals to feelings, emotions, social relationships, and social supports and involve psychotherapeutic modalities such as family support, counseling, and home visits. The last two modalities can help individuals cognitively reframe negative attitudes and learn to become more effective collaborators in their treatment (Dolder et al. 2003; Lacro et al. 2002).

Lacro et al. (2002) also discussed the *health belief model* which involved a summation of a person's susceptibility to illness, his perceived severity of illness, what he would see as benefits of taking health action, and perceived barriers (or costs) and cues to taking action. Improving an individual's assessment of the costs and benefits requires addressing diverse risk factors such as poor insight, negative attitudes toward medications, substance abuse, and the alliance with the therapist. What is the patient's motivation to adhere? In their review medication, side effects were not directly tied to non-adherence but were connected to the cost analysis of medication benefits, "…tipping the cost-benefit ratio against adherence."

All that said, psychoeducational groups are still considered an important part of the treatment armamentarium utilized in hospital settings. Examples of specific psychoeducational topics that can be addressed include the establishment of medication routines, identification of side effects, use of PRN medications if prescribed, negotiating medication changes with physicians, and development of crisis plans centered around medication choices in times of crisis (Noordsy et al. 2000). In addition, educational activities for family members and other care givers have been found to be effective in improving outcomes for both individuals being treated and their significant others (Resnick et al. 2004). With post discharge follow up rates of approximately 50 %,

**Table 7.4** Strategies for ensuring continuity of treatment at discharge

| |
|---|
| 1. Provide enough medication at discharge to last several days to allow for time to have a prescription filled |
| 2. Ask how the patient will obtain the medication on an outpatient basis |
| 3. Find out if the patient has insurance coverage and if it will cover the medication being considered |
| 4. If insurance will not cover the medication, ask about patient's/family's ability to pay out of pocket |
| 5. Choose a medication that the patient will be able to afford or obtain free of charge |
| 6. If patient cannot pay for the medication you believe is indicated, and then contact the pharmaceutical company to see if they will supply medication free of charge or at a reduced cost |

Adapted from Weiden et al. (2007)

steps need to be taken to encourage connection with appropriate outpatient services. One tool that is available is the "Community Reentry Module" that has been shown to be effective in both private and public hospitals (Rossotto et al. 2004). Of course an important step in obtaining and maintaining recovery is cessation of conditions that led to hospitalization (Weiden et al. 2007). See Table 7.4 with regard to medication adherence management.

## Conclusion

This chapter has elucidated the role of pharmacotherapy which can play in assisting individuals on their path to recovery. There is a great deal of research on the "efficacy" of psychotropics, and also potential safety issues that are required in registration trials. Most of our current research, by necessity, looks at large populations with relatively strict inclusion criteria that often do not reflect the reality of people in the community receiving the treatments. There are some efficacy measures that can be indirectly tied to recovery (e.g. time to relapse, symptom reduction), but often the current research falls short of demonstrating our pharmacological armamentarium actually contributes to a person's personal process of obtaining hope, destigmatization, empowerment, self-acceptance, meaningful relationships, gainful employment, independence, and health.

As we continue to develop the operational definitions of "recovery" there needs to be a focus on outcomes that can be utilized in pharmacological research. Measurement of intensity, frequency, and duration of symptoms is of course important in determining efficacy of pharmacotherapeutic agents, but this frequently does not take into account the fluctuating nature of many psychiatric illnesses whose presentations change over time. Moreover, symptom remission alone is an inadequate measure, as often a return to premorbid functioning which is not obtained with mere removal of symptoms. There has to be an assessment of psychosocial functioning, with attention on matters such as work, school, family life, friends, recreation, and independent living.

In putting forward this research agenda, there needs to be a consensus of stakeholders including practitioners, researchers, patients, and family members in determining areas of psychosocial functioning that will be used to establish efficacy in relation to recovery. As with other diseases, when rates of recovery are reported in replicable, reliable, and valid terms, stigma is decreased (Liberman and Kopelowicz 2005). Until such research goals are met, we should fulfill our role in partnering with care recipients to develop evidence-based treatment strategies that minimize adverse effects, are truly individualized, and address amenable aspects of the person's illness he or she finds to be a barrier to his or her recovery.

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