Treatment-Resistant Panic Attacks

Christian Jonathan Haverkampf

***Abstract*—Panic attacks interfere significantly with an individual's life. They have biological, but also psychological and environmental causes. The best therapy is usually a combination of psychotherapy and medication. This article covers several options.**

***Index Terms*—panic attacks, panic disorder, medication, psychotherapy, psychiatry**

I. Introduction

Panic attacks are very common, but can interfere significantly with life. They can lead to situations where an individual loses a job or relationship, or even becomes completely home bound. Besides individual suffering, they cause considerable economic costs to society, compared to healthy persons and to other psychiatric disorders (Andlin-Sobocki and Wittchen, 2005; Batelaan et al.2007; Salvador-Carulla et al.1995).

Panic attacks are intense phases of anxiety and can often occur 'out' of the blue. Still, in any case, exploring and looking into the panic attack can often unearth reasons for the panic attack. Panic attacks are sudden periods of intense fear that may include palpitations, sweating, shaking, shortness of breath, numbness, or a feeling that something bad is going to happen. The maximum degree of symptoms occurs within minutes. Typically, they last for about 30 minutes, but the duration can vary from seconds to hours. There may be a fear of losing control or chest pain. Panic attacks themselves are not dangerous physically.

Anxiety is an emotion characterized by an unpleasant state of inner turmoil, often accompanied by nervous behavior, such as pacing back and forth, somatic complaints, and rumination. It is the subjectively unpleasant feelings of dread over anticipated events, such as the feeling of imminent death. Anxiety is not the same as fear, which is a response to a real or perceived immediate threat, whereas anxiety is the expectation of future threat. Anxiety is a feeling of uneasiness and worry, usually generalized and unfocused as an overreaction to a situation that is only subjectively seen as menacing. It is often accompanied by muscular tension, restlessness, fatigue and problems in concentration. Anxiety can be appropriate, but when experienced regularly the individual may suffer from an anxiety disorder.

People facing anxiety may withdraw from situations which have provoked anxiety in the past. There are various types of anxiety. Existential anxiety can occur when a person faces angst, an existential crisis, or nihilistic feelings. People can also face mathematical anxiety, somatic anxiety, stage fright, or test anxiety. Social anxiety and stranger anxiety are caused when people are apprehensive around strangers or other people in general. Furthermore, anxiety has been linked with physical symptoms such as IBS and can heighten other mental health illnesses such as OCD and panic disorder.

Anxiety can be either a short term "state" or a long term "trait". Whereas trait anxiety represents worrying about future events, anxiety disorders are a group of mental disorders characterized by feelings of anxiety and fear. Anxiety disorders are partly genetic but may also be due to drug use, including alcohol, caffeine, and benzodiazepines (which are often prescribed to treat anxiety), as well as withdrawal from drugs of abuse. They often occur with other mental disorders, particularly bipolar disorder, eating disorders, major depressive disorder, or certain personality disorders.

Anxiety is like any other emotion a heightened mental state with a higher probability of certain conscious processes and behaviors. In anxiety an individual dreads uncertain and often ill-defined events in the future or immediate future. It is not a fear of a specific event, but an unpleasant feeling of heightened arousal which can cause various thoughts and feelings of dread.

A combination of psychotherapy and medication often proves very effective in the treatment of panic attacks. The psychotherapeutic approach is the long-term solution, while medication can often bring a considerable easing of symptoms early on.

Panic disorder has a negative impact on

- well-being and on health perception (Katerndahl and Realini, 1997; Klerman et al, 1991), and is associated with impaired functioning (Kessler et al.2006; Wittchen et al, 1998) and absence from work (Alonso et al, 2004; Kouzis and Eaton, 1994, 1997).
- physical health. It is associated with medical morbidity, including cardiovascular disease (Chen et al.2009; Gomez-Caminero et al.2005; Sareen et al, 2005b; Smoller et al, 2007). Some studies report

Jonathan Haverkampf, M.D. works in private practice for psychotherapy and psychiatry in Dublin, Ireland. The author can be reached by email at jonathanhaverkampf@gmail.com or on his website jonathanhaverkampf.ie.

increased mortality rates in individuals with panic disorder as a result of suicide (Coryell et al, 1982) or cardiovascular disease (Coryell et al, 1982; Grasbeck et al.1996; Smoller et al, 2007).

- suicidal ideation (Cougle et al, 2009; Goodwin and Roy-Byrne, 2006; Lepine et al, 1993; Weissman et al, 1989). However, the impact of comorbid disorders on this association is a matter of debate (Hornig and McNally, 1995) and the evidence that panic disorder causes suicidality remains unclear (Sareen et al.2005a).

II. Panic Attacks as a Complex Illness

A. Reluctance to Seek Help

It may take years before individuals with panic disorder seek help, and only about one third of those affected seek help within the year of onset (Wang et al.2005a), while only half will seek help at all. (Kohn et al.2004; Wang et al.2005b).

As medical explanations are usually considered first, emergency units and somatic specialties are often the first places where individuals seek help. (Hirschfeld, 1996; Katerndahl and Realini, 1995; Leon et al.1995; Rees et al.1998; Salvador-Carulla et al.1995). Misdiagnosis by the general practitioner (Rees et al.1998) or by the cardiologist at the emergency unit is common (Harvison et al.2004; Kuijpers et al.2000). The primary focus on a somatic diagnosis in the case of a first panic attack may be warranted to exclude serious medical conditions. However, a failure of healthcare professionals to identify panic attacks as a serious illness in its own right which requires treatment, prolongs needless suffering in many cases.

B. Correct Treatment

Once the correct diagnosis has been made, delivery of care is often not in concordance with the advice provided in practice guidelines (Bruce et al.2003). It is regrettable that only a minority of individuals with panic disorder receive evidence-based treatment, given the unfavorable long-term course of panic disorder and the impact of panic on daily life. We briefly discuss these aspects below.

C. Treatment-Resistance

A quarter to half of all patients who complete what are considered state-of-the-art treatments do not respond to treatment.

Individual with an earlier age of onset, longer duration of disorder, greater agoraphobic avoidance, and greater functional disability to do more poorly in any form of psychotherapy than patients without these pretreatment characteristics considering the chronicity and severity of their condition.

In a 2003 review Reich concluded that, overall, personality disorders (including but not limited to Cluster C) are a predictor of poor outcome for anxiety treatments across the board, with the possible exception of selective serotonergic reuptake inhibitors.

In the case of anxiety disorders, which are generally considered to respond favorably to cognitive-behavioral treatment (CBT), more than one out of five patients do not reach the criteria for high end-state functioning, and there are questions how long improvements last. The rate is much higher if all those are included who drop out of CBT, which is known to have high drop-out rates. This raises the question how treatment can be improved. CBT is a more structured and often manualized approach which has been criticized for being short on developing understanding for the underlying problems, paying little attention to experienced emotions and failing to tailor the therapy to the specific needs. From a communication perspective, there is too little emphasis on the communication between therapist and patient, which is seen as the curative instrument in many types of psychotherapy.

Most studies on non-response to treatment have focused on medication, usually without any non-pharmacological alternatives. Even when psychological treatments are examined, they are usually administered either directly following or in combination with pharmacology. The problem of nonresponse is particularly challenging when state-of-the-art psychological interventions fail, such as CBT for patients with panic disorder and agoraphobia. Evidence exists that continued exposure can help in some cases. A recent study also addressed this issue in a multisite randomized controlled clinical trial of patients with primary panic disorder and/or agoraphobia (PD/A). These authors examined whether the addition of 9 monthly maintenance (‘booster’) sessions would increase the likelihood of sustained improvement and reduced relapse. Indeed, beyond maintenance of improvements, they also observed symptom reduction in previous nonresponders.

D. Recurrence

The course of panic disorder in the general population may be chronic or recurrent (Batelaan et al.2010a, b; Eaton et al.1998; Kessler et al.2006; Wittchen et al.2008). In addition, comorbid disorders tend to develop during the course of panic disorder (de Graaf et al.2003; Johnson et al.1990; Kessler et al.1998; Wittchen et al.2003). Finally, it should be noted that even when panic symptoms remit, other psychiatric pathology may be present (Wittchen et al.2008).

Despite the availability of treatments with reported efficacy, a substantial number of panic disorder patients do not respond, or only respond partially to treatment. For example, Pollack et

al. (2007b) reported response rates between 70% and 80% and remission rates around 45% during the acute treatment of panic disorder with venlafaxine, thereby underscoring the need for additional treatment strategies to achieve full remission. There are, however, few data to guide clinicians in next-step treatment strategies (Ipser et al.2006). The approach to treatment-refractory patients may consist of optimizing the current treatment, switching to another agent or treatment modality, or augmentation.

III. Medication

Pharmacological agents with sufficient evidence to support their use in the treatment of panic disorder include

- Antidepressants
  - the selective serotonin reuptake inhibitors (SSRIs)
  - the serotonin noradrenaline reuptake inhibitor (SNRI) venlafaxine
  - several tricyclic antidepressants (TCAs) and
  - the irreversible MAO inhibitor (MAOI) phenelzine, and
- Benzodiazepines.

Antidepressants acting on the serotonergic system are effective in treating panic disorder. These include the SSRIs ((es)citalopram, fluvoxamine, fluoxetine, paroxetine, sertraline) (Bakker et al.2002; Hoehn-Saric et al.1993; Lecrubier et al.1997; Michelson et al.1998; Pollack et al.1998; Stahl et al.2003; Wade et al.1997), the TCAs imipramine and clomipramine (CNCPS, 1992; Papp et al.1997), the SNRI venlafaxine (Bradwejn et al.2005; Liebowitz et al.2009; Pollack et al.2007a, b), and the irreversible MAOI phenelzine (Sheehan et al.1980; Tyrer et al.1973).

The first line medication in treating panic attacks over the long-term are usually the serotonin reuptake inhibitors (SSRIs). The serotonin noradrenaline reuptake inhibitor venlafaxine is also an option but may actually increase anxiety and panic attacks in the beginning if the dose is increased to rapidly.

While the antidepressants can take weeks to work, co-administration of benzodiazepines can be considered for the meantime.

Comparable efficacy has been shown for

- (imipramine) and benzodiazepines (alprazolam, clonazepam) (Van Balkom et al, 1995)
- SSRIs and TCAs (Bakker et al, 1999, 2002; Lecrubier et al, 1997; Otto et al, 2001; Wade et al, 1997), and
- when comparing various SSRIs (Dannon et al, 2007)

However, over time the SSRIs, such as escitalopram, have become a first choice, because of their better risk profile as compared to the TCAs. The capacity for tolerance and dependence should rule out benzodiazepines as a regular long-term medication. SSRIs and venlafaxine. On the other hand. are effective in acute and long-term treatment, have an acceptable side-effect profile, acceptable drop-out rate, and are effective in comorbid depression.

In one study, a high dosage of venlafaxine (225 mg) proved to be superior to 40 mg paroxetine on the primary outcome measure (percentage of patients free from full-symptom panic attacks) and on one of the secondary outcome measures (improvement on the Panic Disorder Severity Scale) (Pollack et al, 2007). Since there are several psychopharmacological options, the side-effects and risks involved, drop-out rates, the time of onset of action, and efficacy in comorbid symptomatology can play an important role in picking the right antidepressant.

The irreversible MAOI phenelzine should be prescribed only in case of severe and treatment-refractory panic disorder given the side-effect profile and risks involved, and the high drop-out rates on that medication.

A. Antidepressants

Antidepressants are effective for a range of anxiety disorders and depressive disorder, which are commonly comorbid with panic disorder (Bandelow et al.2008). Particularly a comorbid depressive disorder can worsen the panic attacks. For all antidepressants, onset of action in panic disorder is relatively slow. As a result, an assessment of outcome should be made only after several weeks of treatment.

The SSRIs (Holland et al, 1994; Lecrubier and Judge, 1997; Lepola et al, 1998) and the TCAs (Curtis et al, 1993; Lecrubier and Judge, 1997; Mavissakalian and Perel, 1992) all seem to remain effective in the treatment of panic disorder over the long-term with follow-up periods of up to two years.

Given the slow onset of action and the potential for increased anxiety during the initial phase of treatment with antidepressants, in clinical practice particularly in the case of venlafaxine and the SSRI sertraline, temporary co-administration of a benzodiazepine should be considered.

1) Serotonin Reuptake Inhibitors (SSRIs)

The SSRIs escitalopram and paroxetine (extended release), and the SNRI venlafaxine (extended release) have been thoroughly investigated in panic disorder.

In a ten-week randomized controlled, double-blind trial (total n=366, n=128 with escitalopram), escitalopram showed to be more effective than placebo (Stahl et al.2003), even though the dose was quite low at 5-10 mg. In another study, three double-blind placebo-controlled trials investigating paroxetine CR were pooled for a total study population of 889

panic disorder patients. Paroxetine CR (25–75 mg/d) was superior to placebo in reducing symptoms (Sheehan et al, 2005).

The most common side-effects of the SSRIs include headaches, irritability, gastrointestinal complaints, insomnia, sexual dysfunction, weight gain, increased anxiety, drowsiness and tremor. However, increasing the dose very slowly is in clinical experience often helpful.

To prevent side-effects, it is advised to start treatment with antidepressants at a low dosage. Of special importance is the finding that panic symptoms often increase in the first weeks of treatment with SSRIs, venlafaxine or TCAs. This may be partly due to misinterpreting physical side-effects as symptoms of a panic attack. Psycho-education should aim to prevent such misinterpretations, and slow dose titration is recommended. To lower anxiety symptoms and to achieve a more rapid stabilization of panic symptoms, temporary addition of benzodiazepines during the initial phase of antidepressant treatment can also be considered (Goddard et al.2001; Pollack et al.2003).

During SSRI treatment of panic disorder 18% of patients drop-out prematurely (Bakker et al, 2002). However, some agents may have lower drop out rates: Paroxetine (11%, Sheehan et al.2005), escitalopram (6.3%, Stahl et al.2003) and venlafaxine (1-12%, Kjernisted and McIntosh, 2007).

2) Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

The SNRI venlafaxine XR (75–225 mg/d) has been found significantly more effective than placebo in several randomized controlled, double-blind trials (Bradwejn et al, 2005; Liebowitz et al, 2009; Pollack et al, 2007; Kjernisted and McIntosh, 2007). A 6-month placebo-controlled discontinuation study found that time to relapse was significantly longer in the venlafaxine XR group than the placebo group (Ferguson et al, 2007).

The most common side-effects of venlafaxine as reported in panic disorder patients are nausea, dry mouth, constipation, anorexia, insomnia, sweating, somnolence, tremor and sexual dysfunction. Monitoring of blood pressure is advised given the increase in blood pressure that is sometimes observed.

3) Tricyclic Antidepressants

TCAs may have a slower onset than SSRIs (Lecrubier et al, 1997). In addition, TCAs have a less tolerable side-effect profile than SSRIs given that they have more anticholinergic effects, and are generally less safe than SSRIs. Finally, reported drop-out rates are higher for TCAs compared to SSRIs (Bakker et al.2002).

Specific concern is needed when treating elderly patients with TCAs as orthostatic hypotension may result in falls. In addition, arrhythmias may occur in patients with pre-existing cardiac conduction abnormalities, and in case of an overdose.

In TCAs the most commonly reported side-effects in panic disorder patients are anticholinergic effects, increased sweating, sleep disturbance, orthostatic hypotension and dizziness, fatigue and weakness, cognitive disturbance, weight gain, and sexual dysfunction.

The dropout rates for the TCAs seem higher than those of SSRIs at 30% (Bakker et al.2002).

B. MAO Inhibitors

Even reversible MAO inhibitors tend to have side effect and risk profiles that are inferior to newer antidepressants. They should only be considered in treatment resistant cases where different antidepressants and antidepressant combinations have been tried before. Due to the unfavorable side-effect profile of MAOIs, drop-out rates are high.

C. Benzodiazepines

The benzodiazepines alprazolam, clonazepam, diazepam and lorazepam are superior to placebo in the acute phase treatment of panic disorder (CNCPS, 1992; Van Balkom et al.1995, 1997). Benzodiazepines have a fast onset of action (Burrows & Norman, 1999), often working within half an hour. Even though many panic attacks are over by then, the psychological effect of having a stand by medication that can switch of the anxiety relatively quickly can help break the vicious cycle of anxiety leading to more anxiety.

Controlled studies with alprazolam for up to 32 weeks (Ballenger, 1991; Burrows et al, 1993), and an open study with clonazepam lasting over one year (Pollack et al, 1986) showed that these benzodiazepines are efficacious in maintenance treatment. However, in clinical practice benzodiazepines tend to lose their effectiveness over time, requiring dose increases and can ultimately lead to dependency with withdrawal symptoms when stopped. While dose escalation may not be a common consequence of long-term benzodiazepine use, problems when discontinuing benzodiazepines are frequently reported, especially during the last half of the taper period (APA, 2009).

Benzodiazepines may even induce anxiety and depression over the long-term if used regularly. However, this does not seem to apply if they are used irregularly once off to treat acute anxiety, even over the long-term.

Side-effects of benzodiazepines include sedation, fatigue, ataxia, slurred speech, memory impairment, and weakness (APA, 2009). Trying the lowest dose first can lower the side effects.

Benzodiazepines are also generally thought to be ineffective for comorbid depressive disorders (Bandelow et al.2008). Since anxiety and at least mild forms of depression quite often

go together, an antidepressant is often the more effective - and safer - regular treatment option. Insufficient data are available to determine whether combining benzodiazepines and psychotherapy is beneficial or not (Watanabe et al.2007).

D. Duration

Maintenance pharmacotherapy has consistently shown to prevent relapse when compared to medication discontinuation (Donovan et al, 2010). Often, it also requires considerable lengths of time for the full anti-anxiety and anti-panic attack effect of medication (Ballenger, 2000; Lecrubier and Judge, 1997). There can also be a psychological learning effect that the brain unlearns to be anxious about becoming anxious.

Reducing the vulnerability to relapse should be a main goal of treatment (Andrews, 2003; Batelaan et al, 2010; Fava and Mangelli, 1999). Discontinuation of pharmacotherapy frequently results in relapse (Ferguson et al, 2007; Lecrubier and Judge, 1997; Lotufo-Neto et al, 2001; Marks et al, 1993; Mavissakalian and Perel, 1999; Noyes et al, 1989, 1991; Rapaport et al, 2001; Spiegel et al, 1994). 37% of patients experienced a relapse within ten weeks of discontinuing clomipramine, and another 43% of patients within about eighteen months (Lotufo-Neto et al, 2001), and half of those who discontinued venlafaxine relapsed within six months (Ferguson et al, 2007). However, relapse occurred in one study as frequently after six months of treatment as it did after 12–30 months of treatment (Mavissakalian and Perel, 2002). It was also reported that even after three years of sustained remission while taking medication, relapse occurred more often and earlier in those who discontinue medication compared to those who continue pharmacological treatment (Choy et al.2007).

Many remitted patients discontinue antidepressant treatment. Studies investigating treatment adherence of anxiety disorder patients and, more specifically of panic disorder patients, reported that more than half of the patients are non-compliant or interrupt treatment within several months to years (Stein et al, 2006; Toni et al, 2004).

Psychological processes probably play a significant role in the state of compliance. If a prescriber keeps a patient well informed and conveys to patients that they are well understood and cared for, compliance is easier to achieve than in ten minute prescribing. This is another reason why medication and psychotherapy or counseling should go hand in hand. One without the other risks inferior results.

Whereas the guideline from the American Psychiatric Association refrains from recommendations (APA, 2009), most guidelines refer to expert consensus and suggest continuation for at least a year (Andrews, 2003; Bandelow et al.2008; LSMRG, 2009), although a shorter period has also been suggested (Baldwin et al.2005; CPA, 2006).

When medication is being discontinued, consensus advice is to taper down the medication gradually over weeks to months (APA, 2009; Andrews, 2003; Baldwin et al.2005; LSMRG, 2009) to reduce the likelihood of discontinuation symptoms and to monitor for early signs of relapse. In several cases, it may even be helpful to stay at a longer dose for a significant length of time, possibly even a year or longer, before discontinuing the medication altogether.

Predictors for relapse should always be considered, because those at the highest risk for relapse may benefit most from long-term maintenance treatment, and it can be hypothesized that patients at the highest risk for relapse are better motivated for long-term maintenance treatment. In addition, costs of long-term maintenance treatment for those at highest risk to relapse may well be acceptable given the costs associated with recurrence of panic disorder.

E. Metabolization and Compliance

If medication is ineffective or only partially effective, the first step is to assess if there are any compliance problems. When asking if the patient has any questions about the medication and how he or she gets along with it, one should notice quite quickly if there are potential compliance problems. If patients do not seem to fully understand why they are on a specific medication, or any medication at all, this needs to be explained. The patient should also be encouraged to talk about own fears and anxieties regarding the medication. Some issues are often not addressed, such as sexual side effects or a patient's fear that one's personality could change on the medication. It is imperative that prescriber and patient work together and trust each other enough to share information. Empathy and a commitment to help the patient on the prescriber's side needs to be communicated.

F. Dose Adjustment

In many cases when patients feel the antidepressant is helping less, the dose may have been too low from the beginning. Also, when patients experience that the medication helps less in certain, often more stressful, situations, the dose may often be too low.

There is some debate about the additional benefit in raising the dose. A small study reported that an increased dosage of a SSRI was no more effective than continuing the previous dosage (Simon et al, 2009), a finding that is in line with recent research on the absence of additional effects when increasing the SSRI dose in depressed patients (Ruhe et al.2009). However, in clinical practice often raising the dose can help against anxiety and panic attacks, depending on the medication. This is frequently seen, for example, when raising escitalopram from 15 mg to 20 mg.

G. Switching

Switching within or between classes of pharmacological agents seems a reasonable option. If one begins with an SSRI, a course of action could to switch to

- another SSRI
- the SNRI venlafaxine
- clomipramine
- a MAO inhibitor, if the potential benefits appear to outweigh the substantial risks

H. Augmentation

Rather than switching to another medication, augmenting with a substance from a different class can be helpful.

1) Second generation antipsychotics

Augmentation of antidepressants with an antipsychotic has been suggested for refractory panic disorder patients (Hoge et al, 2008; Saito and Miyaoka, 2007; Sepede et al, 2006; Simon et al, 2006), which is also being used quitter frequently in clinical practice. Risk-benefit ratios should be carefully considered given the adverse effects of antipsychotics. Quetiapine and olanzapine, for example appear to be helpful in the treatment of panic attacks in anxiety. Since they can have serotonergic effects one needs to be careful when combining them with serotonergic antidepressants.

2) GABA analogues

Pregabalin and gabapentin are also used to enhance the anxiety reducing effects of antidepressants. Especially in more physically felt anxiety and panic attacks, they can be helpful. There is some empirical data that suggests abuse of pregabalin is much less an issue in patients who suffer from anxiety and panic attacks than in those without this diagnosis and particularly in those with prior substance abuse.

I. Other Medication

In addition, a wide range of other pharmacological agents has been suggested for the treatment of panic disorder. These include SNRIs other than venlafaxine (Blaya et al, 2007; Simon et al, 2009), the selective noradrenergic reuptake inhibitor reboxetine (Bertani et al, 2004; Dannon et al.2002; Seedat et al.2003; Versiani et al, 2002), GABAergic treatment including vigabatrin and tiagabine (Pande et al, 2000; Zwanzger and Rupprecht, 2005; Zwanzger et al, 2009), the reversible MAOI moclobemide (Kruger & Dahl, 1999; Loerch et al, 1999; Ross et al, 2010; Tiller et al, 1999; Uhlenhuth et al, 2002), other antidepressants including mirtazapine, buproprion, trazodone (APA, 2009), anticonvulsants (Mula et al, 2007; Papp, 2006), the antipsychotic olanzapine (Hollifield et al, 2005), and antihypertensives (APA, 2009). None of these agents can be considered as first-line options for the pharmacological treatment of panic disorder because they are insufficiently investigated or because results were inconsistent. A clinician could potentially consider prescribing these agents in treatment-refractory patients, prioritizing those agents for which there is the most data on efficacy and tolerability.

The agents for which there is most data on efficacy and tolerability are the SNRIs milnacipran and duloxetine and the selective noradrenergic reuptake inhibitor reboxetine. This is not surprising given the efficacy of the SNRI venlafaxine in the treatment of panic disorder and the noradrenergic role in the pathophysiology of panic disorder. Small open-label studies showed positive results for the SNRIs milnacipran (Blaya et al.2007) and duloxetine (Simon et al.2009a). Reboxetine has been investigated in several small studies. In a single-blind, cross-over study, reboxetine was as effective as citalopram with regard to panic, although less effective than citalopram with regard to co-occurring depressive symptoms (Seedat et al.2003). In a single-blind randomized trial (n=68), paroxetine showed larger effects on panic attacks than reboxetine, but no differences were found on anticipatory anxiety and avoidance (Bertani et al, 2004). In a double-blind randomized, controlled trial reboxetine was more effective compared to a placebo group (Versiani et al, 2002). Finally, in a small open-label study, reboxetine showed positive effects for patients who had not responded to a SSRI (Dannon et al.2002). Given these preliminary results, both these SNRIs and reboxetine might be an option when prescribing off-label agents in treatment-refractory patients.

IV. Psychotherapy

There are several psychotherapeutic approaches which have been used with at least some success in panic attacks. Like medication, one benefit is that also comorbid conditions can be addresses, often to a greater degree than with medication.

The incremental efficacy of combined psychotherapy and antidepressant treatment was investigated in a Cochrane review including 21 trials in panic disorder (Furukawa et al, 2007). The authors concluded that in the short term, combined therapy was superior to medication alone, as well as to psychotherapy alone. These findings were irrespective of the kind of antidepressant, irrespective of the presence of agoraphobia, and irrespective of the presence of comorbid depression. Six months after terminating treatment, combination therapy was more effective than medication alone, but was as effective as psychotherapy alone. This finding should be interpreted with some caution, given the naturalistic nature of the follow-up period, with a substantial proportion of patients receiving treatment of some kind (Furukawa et al, 2007). The psychotherapy used in most cases was CBT.

CBT and psychodynamic therapies have shown effectiveness in the treatment of anxiety and panic attacks. Both have theories about why they help. The former sees learning processes and certain thought patterns as central, the latter the processing of content at various levels of consciousness and certain processes between therapist and patient. However, they both place little emphasis the communication processes between therapist and patient and inside each that often in clinical processes are what brings about substantial change in the right direction. (Haverkampf, 2017a) Communication-Focused Therapy (CFT) in this respect may be seen as a standalone therapeutic approach or combined with one of the other two approaches.

Outcome Predictors

Higher emotional awareness and lower global illness ratings at baseline predicted more change in treatment for patients with panic disorder receiving either panic-focused psychodynamic psychotherapy or CBT (Beutel et al, 2013). Cluster C does not seem to be a predictor of poor outcome for psychotherapy (Porter and Chambless, 2015). However, they may improve more in psychodynamic psychotherapy than CBT (Barber & Muenz, 1996; Milrod, Leon, Barber, et al., 2007), while the reverse may be true for obsessive-compulsive personality disorder.

Patients with lower abilities for reflection and introspection may benefit more from CBT than from the psychodynamic oriented psychotherapies. However, this plays less of a role in the communication-focused therapy model developed by the author which focuses also on insight but uses an easier to understand model of internal and external communication patterns. (Haverkampf, 2010c, 2010b)

The patient's past history often influences which therapy model is picked but technically it may play a lower role. In CBT and interpersonal psychotherapy (IPT) the work is mostly focused on the present, while in psychodynamic oriented schools of therapy the past takes in more space. In communication-focused therapy (CFT) the present and the future play a greater role, while the past helps to understand an effect in the present.

Belief in the effectiveness of therapy is important, which applies to other areas in medicine to at least a lesser degree as well. Psychotherapy is no exception. A primary care provider who makes the patient understand his own skepticism of everything psychological may be unaware of the damage done to the treatment prospects of the patient who may never seek help for a mental health condition at all or approach it with 'I just need to check this off' attitude. Individuals who expect more benefit from therapy at the outset of treatment are likely to make greater gains in any form of psychotherapy (Constantino, Glass, Arnkoff, Ametrano, and Smith, 2011).

It is important for all healthcare professionals involved to provide a setting that is supportive of a course of psychotherapy, which includes particularly primary care physicians. The working relationship between therapist and patient and the positive outcome of a therapy are related (Huppert et al, 2014).

In studies of CBT for various disorders, both the quantity and quality of homework completion is associated with better outcome (Kazantzis et al., 2016). It seems likely that expectancy might also affect the level of engagement in challenging activities in session such as interoceptive exposure in CBT and interpretation of intrapsychic conflict and the transference in PFPP.

Relapse Prevention

Providing psychotherapy to panic disorder patients may be beneficial in enhancing the long-term outcome for several reasons, the most important reason being that the effects of CBT may be maintained over time (Bakker et al.1998; Fava et al.2001; Oei et al.1999; Peter et al.2008). In addition, some evidence indicates that a CBT relapse-prevention program provided after acute-phase treatment prevents relapse in patients with panic disorder (Wright et al, 2000) and that adding brief psychodynamic psychotherapy to clomipramine treatment may reduce relapse rates in panic disorder (Wiborg and Dahl, 1996). Finally, a few studies have shown that CBT may also prevent relapse or worsening of panic in patients who discontinue pharmacological treatment (Bruce et al.1999; Choy et al, 2007; Furukawa et al.2007; Schmidt et al, 2002; Spiegel et al, 1994; Whittal et al, 2001).

A. Cognitive-Behavioral Therapy (CBT)

CBT is effective in panic disorder (Barlow et al, 1989, 2000; Öst et al, 2004; Furukawa et al, 2007), and positive effects have been reported for CBT in studies with panic disorder patients who failed to respond adequately to pharmacological treatment (Rodrigues et al.2011).

Interoceptive exposure is frequently used, in which patients are exposed to exercises that evoke the physical sensations associated with a panic attack, such as hyperventilation, in order to experience that the worst expected outcome (e.g., dying) does not occur (i.e., "expectancy violation").

Approximately 40-90% of patients treated with CBT are panic free directly after treatment (Bakker et al., 1999), while it is possible that the effects are not as long lasting as in insight or communication focused approaches. Thus, so called 'booster sessions' are frequently necessary within months or half a year. Also, a sizeable group of patients still needs additional treatment after CBT because some patients do not benefit, while others do not make a full recovery or develop other affective disorders (Van Balkom et al., 1996; Bakker et al., 1999).

Several studies have shown that the quality of life (QOL) for patients with PD improves after CBT (Telch et al., 1995;

Davidoff et al., 2012). However, treatment effects of CBT seem to vary significantly with various factors, such as comorbidity or whether exposure treatment is included (Bakker et al., 1999; Rief et al., 2000). Also, earlier age of onset and a longer duration may make CBT less successful. Higher levels of pretreatment agoraphobic avoidance, lower expectancy of change, and greater pretreatment functional impairment consistently seem to predict worse response to CBT (Porter and Chambless, 2015).

CBT tends to be highly manualized. For example, Barlow and Craske's Panic Control Therapy protocol (Craske, Barlow, & Meadows, 2000) includes

- psychoeducation about anxiety and panic attacks
- identification and correction of maladaptive thoughts about anxiety and panic
- training in relaxation exercises, such as slow, diaphragmatic breathing, muscle relaxation to also reduce the levels of general anxiety
- and exposure to bodily sensations designed to mimic those experienced during panic.

All sessions are followed by homework assignments and readings. In vivo exposure via homework assignments can be introduced for those patients with significant agoraphobic avoidance. A review and relapse prevention follow towards the end of the treatment program.

The treatment programs also include

- Cognitive therapy in which the patients learn to recognize their automatic, anxious thoughts and formulate alternative, more adaptive thoughts
- In vivo exposure consisted of learning patients to cope with the anxiety experienced during situations or activities that are feared and avoided by using an anxiety hierarchy

(Kampman et al., 2004).

B. Psychodynamic Therapy

Panic-Focused Psychodynamic Psychotherapy (PFPP) is a manual-based treatment (Milrod et al., 1997) rooted in the assumption that panic symptoms have a psychological meaning and that uncovering these unconscious meanings will lead to relief. The therapist explores the circumstances and feelings surrounding panic onset, the personal meaning of panic symptoms, and the feelings and content of panic episodes. PFPP aims to lessen vulnerability to panic by helping patients understand and alter core unconscious conflicts, which are often identified and understood through their emergence in the transference. Frequent themes include conflicts over separation and autonomy; recognizing, managing, and expressing anger; and guilt. Termination, addressed prominently in the last third of treatment, permits patients to re-experience conflicts directly with the therapist so that underlying feelings can be articulated and rendered less frightening.

Panic-focused psychodynamic psychotherapy (PFPP) has been found to be effective in the treatment of panic disorder (Milrod, Leon, Busch et al., 2007; relatively small sample size). In several other papers Milrod and colleagues sought to examine moderators in their study, but in light of their small sample appropriately did not employ statistical tests of their hypotheses (Kraemer, Wilson, Fairburn, &Agras, 2002).

The difference in favor of PFPP was even greater for patients whose panic disorder onset was not precipitated by a recent interpersonal loss (Klass et al., 2009) and for those with a comorbid Cluster C diagnosis (Milrod, Leon, Barber, et al., 2007). Patients with and without a comorbid Cluster B diagnosis appeared to fare similarly well in each treatment, but the number of Cluster B patients was so small as to limit any conclusions (Milrod, Leon, Barber, et al., 2007).

C. Acceptance and commitment therapy (ACT)

Acceptance and Commitment Therapy (ACT) is a cognitive-behavioral therapy that teaches psychological concepts, such as mindfulness, acceptance, cognitive defusion (flexible distancing from the literal meaning of cognitions), and other strategies to increase psychological flexibility and promote behavior change consistent with personal values. Within ACT, psychological flexibility is defined as the capacity to make contact with experience in the present moment, and – based on what is possible in that moment – to persist in or change behavior in the pursuit of goals and values. Clinical studies and RCTs provide evidence that ACT is effective for a wide array of disorders, including primary treatment for anxiety disorders, such as social anxiety disorder, panic disorder, and mixed anxiety disorders.

A unique aspect of ACT is its focus on helping patients learn to interact more flexibly with their symptoms (e.g., simply observe them as opposed to trying to eliminate them) and to continue pursuing their values and life goals even in the presence of symptoms. Some patients seem to respond better generally to an approach focused at well-being than at exposure.

ACT is therefore especially suitable to help treatment resistant patients, precisely because the possibility that symptoms may persist has been elegantly integrated into its treatment rationale. Accordingly, this therapy helps patients abandon their longstanding, unsuccessful struggle with their symptoms. This stance allows for the possibility of meaningfully improving patients' lives, even when symptoms persist, and suggests that ACT could be a particularly efficacious and viable treatment option for patients who did not respond to state-of-the-art treatments

ACT specifically aims to alter the struggle with longstanding symptoms by undermining the unnecessary struggle with internal psychological barriers in order to engage with what is important in one's life. In particular, not suppressing uncomfortable thoughts and emotions (i.e., acceptance) and not taking anxious thoughts and feelings literally (i.e., defusion) can show improvement. Large effects have also been reported on measures of mindfulness and general difficulty with unhelpful emotional regulation.

Several studies show that acceptance- and mindfulness-based interventions achieved better outcomes for patients with comorbidity, whereas traditional CBT fared better for patients with only one disorder. Adding mindfulness training also seems to lead to lower drop-out rates.

D. Eye Movement Desensitization and Reprocessing (EMDR)

Eye Movement Desensitization and Reprocessing (EMDR) therapy is a treatment procedure for patients who suffer from past traumatic experiences in the present (Shapiro, 2002). In EMDR therapy the focus is on resolving disturbing memories of distressing or traumatic events by focusing on the memory while making eye movements at the same time. Besides CBT, EMDR is recommended as a first-line treatment for psychological trauma (Bisson et al, 2007).

There are several reasons why EMDR could be useful in the treatment of PD. Firstly, panic attacks likely occur unexpectedly, are experienced as distressing, cause a subjective response of fear or helplessness, and can be considered life threatening (McNally and Lukach, 1992; Hagenaars et al, 2009). Secondly, there are indications that panic memories in PD resemble traumatic memories as seen in PTSD (Hagenaars et al., 2009). Thirdly, there are indications that PD often develops after one or more distressing life events (Faravelli and Pallanti, 1989; Horesh et al, 1997).

A decrease in panic complaints and anticipatory anxiety in EMDR-treated patients has been found (Goldstein and Feske, 1994; Feske and Goldstein, 1997; Goldstein et al., 2000). Goldstein et al. (2000) showed that EMDR was superior to the waitlist condition on panic and agoraphobia severity, albeit no significant change was apparent on cognitive measures or on panic attack frequency. A pilot study comparing 12 sessions of EMDR to CBT for PD, found no differences between both treatments, except that EMDR resulted in significantly less frequent panic attacks (Faretta, 2013).

E. Communication-Focused Therapy (CFT)

Communication-focused therapy (CFT) is a therapeutic approach developed by the author, which focuses on communication as the underlying process of many psychotherapeutic approaches.

Communication-Focused Therapy (CFT) was developed by the author to focus more specifically on the communication process between patient and therapist. The central piece is that the sending and receiving of meaningful messages is at the heart of any change process. CBT, psychodynamic psychotherapy and IPT help because they define a format in which communication processes take place that can bring about change. However, thy do not work directly with the communication processes. CFT attempts to do so.

Panic attacks are usually a signal that something is out of sync in the life of the patient. Individuals often are more likely to encounter anxiety when there is an underlying feeling that something or things in their life are 'out of sync'. This can occur in many situations in professional or private realms. A patient with anxiety may not be aware of the signal directly but of the anxiety which is triggered by it. Anxiety then makes it even more difficult to connect with oneself or others to gain insight into what is causing the anxiety. Communication on the inside and on the outside suffers in states of anxiety which makes it more difficult to resolve the issues that have led to the higher anxiety states.

A life is 'out of sync' if it does not correlate anymore with one's values, basic interests, aspirations, true needs, wants and desires. Through one's behaviors and thoughts one finds out more about oneself, but one does not have to know these parameters consciously in order to have a sense for what is meaningful in one's life, which, however, requires being connected emotionally to one oneself in a meaningful way. Individuals who are suffering from burnout, for example, often experience this disconnect.

Areas which people often feel anxious about are where there has been an issue with their interpersonal interactions in the past. Early traumata, like a disappearing or abusive parent, stay unresolved. For example, if a parent feels fearful and angry with himself and this is picked up by a child, the latter may decode these messages correctly in that the parent is angry, but since the parent may not be conscious about it, the child does not pick up on the second important half of the message, that the parent has a problem with himself and his issue is unrelated to the child. Of course, one can learn to pick up on the self-blame and frustration of the parent, and therapists should become experts at reading between the lines in this fashion, but it requires experience, reflection and insight into transference and counter-transference phenomena, for example, to use the psychoanalytic terms.

1) Using Communication to Reverse the Disconnect

Communication is an autoregulatory mechanism. It ensures that living organisms, including people, can adapt to their environment and live a life according to their interests, desires, values, and aspirations. This does not only require communicating with a salesperson, writing an exam paper or watching a movie, but also finding out more about oneself, psychologically and physically. Whether measuring one's strength at the gym or engaging in self-talk, this self-exploration requires flows of relevant and meaningful

information. Communication allows us to have a sense of self and a grasp of who we are and what we need and want in the world, but it has to be learned similar to our communication with other people.

The disconnect with oneself and others can be reversed quite easily. The fears that are connected with it are often the hardest obstacles to overcome. Various CFT techniques are described elsewhere. (Haverkampf, 2010b, 2017b, 2017c, 2018a) Through greater awareness for the communication patterns and information flows one uses with oneself and others, the fears to experiment with them is usually reduced and meaningful change can happen. This can be achieved in a therapeutic setting through working with the external communication, which is also the only one visible to a therapist. Reflecting on the external communication is then transposed to the inside, where the same skills can be used with the internal communication. It is important to realize, however, that these observation processes have to come from the patient to be successful. This is why manualized therapies are unhelpful in this regard, because the patient has to find a style of communicating about communicating, or reflecting, which is his or her own. Thus, in a therapeutic setting the therapist should not merely supply the own style of thinking about communication, but support the patient in finding back, or forward, to his or her own style.

2) *Focus on the Now*

Communication bridges the present and the future, as well as the past and the present. It helps store information or transmit it to people somewhere else we have never met. The principle behind it is that information will be transmitted on as long as the sender feels the message is relevant to another and/or oneself. Information endures as long as it is relevant to the people who communicate it. In an emergency information can get through because it is relevant, and the sender can expect help as long as he or she believes that the own emergency situation is relevant to others. The ability to communicate by various means, spoken, gestures, email, smoke and so forth, can thus make people feel safe, if they trust in their own skills and that their message will be relevant and meaningful to another. Patients with anxiety often have lower faith in either or both.

Memories of past experiences and the emotions associated with these past experiences can have an impact on how one feels in the present and the strategies one uses to act and interact in everyday life. Better internal communication allows to gain an understanding for any emotions that still have not found closure and other issues that have not been resolved yet. However, fears may prevent this, such as the fear to get lost in the past without resolving anything in a constructive way.

When patients learn to better connect with themselves emotionally, cognitively and in all other communicative ways, the fear usually of confronting unresolved issues usually decreases. The reason is that a better connection with oneself also makes the own resources more accessible, and hence visible, while making the sense of self feel more present and more clearly defined. These processes may not happen in complete synchrony, which can require a greater emphasis on support in therapy, whenever the pain is clearer than the positive resources. However, usually the process of connecting with oneself in itself makes the patient feel stronger an in more in charge of his or her owner inner life.

3) *Embracing Change*

A positive expectation of change plays a significant role in the effectiveness of therapy. Focusing on a process which is also easily observable and understandable by the patient, communication, individualization of treatment and clear structures can make the patient more hopeful about change in the future.

Anxiety and Panic Attacks are related to how people communicate with themselves and with others. They often occur when a relationship breaks apart or some other interpersonal change or issue causes. The result is often communicative patterns that are maladaptive to the individual. These changes in communication patterns are what causes then the problems to the individuals.

Often, there are already maladaptive communication patterns before, that cause the problems in the relationship or interpersonal interactions. These patterns can be analyzed and changed. Another important element is that communication can also take place on the inside of the individual.

Often, therapeutic work is done on lowering the anxiety levels to certain thoughts or stimuli. However, the believability and what they mean to the individual is often more important. Exposure is thus limited in what it can achieve. A change in perspective, however, can lead to more enduring change in various everyday life situations. This in turn depends on changes in internal and external communication.

4) *Reducing Subjective Uncertainty*

In life, one has to live with uncertainty. Uncertainty just means that there is no manual in the beginning and there are still unknowns which leave room for excitement and exploration. Life is a learning experience. An individual suffering from anxiety may have areas in life where she thrives on excitement, and other areas where images of worst case scenarios cause her to freeze when she just considers a change in action or any action at all. Uncertainty to someone suffering from anxiety seems to be bearable in some areas and avoided in others. Often, the areas where it is not tolerated feel meaningful only to the person suffering from anxiety.

Anxiety often occurs when the confidence to communicate one's needs, wishes or feelings is compromised. Humans learn early on that their well-being and survival depends on

communicating their needs to others, originally their parents, later their work colleagues, friends, and romantic partners. Communication makes us feel safer in the world, because it is the main tool with which we fulfil our needs, values and aspiration. (Haverkampf, 2010a) Thus, an increase in the confidence in one's internal and external communication abilities reduces the uncertainty and lack of security experienced in the world, which also lowers anxiety.

Anxiety requires a certain amount of uncertainty. It often occurs in situations when there is uncertainty about external events or situations, often interpersonal ones, or uncertainty about one's own feelings, mental or physical states. Without uncertainty about oneself or the world around there is no room for anxiety. However, this it is impossible to achieve a state of complete certainty, which would also make any change or progress impossible. The environment does not even have to change to make changes in the individual necessary. For example, if one develops greater insight in something in the environment or in oneself, changes in one's thoughts, perspectives, behaviors and interactions may become necessary. Change helps people not only to survive but also to make the best out of their place int the world. The more open an individual is to change and the easier it is for one to implement the change the less reason there is for anxiety. Accepting that there is a level of uncertainty in life makes it easier to develop the tools to deal with it. This raises self-confidence, the sense of efficacy in the world, self-awareness and lowers anxiety.

Information reduces uncertainty, and communication is the mechanism which provides information. Meaningful information has the potential to bring about adaptive and beneficial changes in an individual, even if it only leads to a change in perspective. The information can be about the environment or about oneself, come from the outside or the inside. Communication-focused therapy (CFT) has at its objective to improve the internal and external communication to lead to a reduction in mental health symptoms, greater satisfaction and contentment, as well as greater success in the world to get one's needs, values and aspirations met. Especially in cases of anxiety and panic attacks, an ability to deal with and integrate uncertainty into one' s life is very effective in reducing the symptoms.

5) Countering Avoidance

Anxiety can lead to avoidance, which in turn can attach even more anxiety to the situations or behaviors which are being avoided. In social situations, not interacting with others deprives the person of continuously updating and honing the skills and confidence of interacting with others. Avoidance can thus lead to an increase rather than a decrease in anxiety in the long-run.

Since helpful communication, an open exchange of meaningful messages internally and externally, reduces anxiety, an avoidance of sources of meaningful information increases anxiety. Unfortunately, avoidance may not be self-correcting and lead into a vicious cycle in which ever greater anxiety leads to ever greater avoidance to the point where a patient can become house or even bed bound, and a normal work or private life are no longer possible.

6) Building the Sense of Self

Trust in oneself is built through communication with oneself and others and an expectation that one can get one's needs, wants and aspirations satisfied through these interactions. Trust is thus a two-way street as it depends on the own competency to send messages about one's needs, wants and aspirations into the world in a way that is most likely to get a result and for the world to respond in the way expected. From a communication viewpoint many parts to have to fall in place, from the own identification of what one truly needs and values to other people's own sense of their needs, values and aspirations. What makes the match possible are internal and external communication. Practicing communication. Internally and externally, can therefore build trust.

Building trust in oneself is an important component in the treatment of anxiety. A first step usually is that the patient can identify own needs and wishes, which is an important step in reconnecting with oneself. Feeling this reconnection is ultimately what builds more trust. If one is more connected with something, it becomes more predictable and closer to oneself.

7) Restoring Meaning

Individuals suffering from anxiety and panic attacks often see less meaning in the things they do. In therapy an important part is to rediscover meaning, and find it in the things that are relevant to the patient. Relevant is anything that is close to his or her values, basic interests, aspirations, wants, wishes and desires. Meaning has the potential to bring about change, and meaningful information is what the individual should learn to select for more. Anxiety often leads to a withdrawal from meaningful information in the form of social withdrawal or greater rigidity in one's daily activities by increasingly shutting out sources of valuable information. In a therapeutic setting this should be reversed by encouraging the patient to ask questions again, by having an inquisitive mind in the world which always looks out for meaningful information. The goal is not to shut off the constructive facilities of the mind. Many forms of meditation, for example, thus not have as the objective to turn off the mind but to actually find more meaning in the world in the form of information which brings about a beneficial change. A greater openness to meaningful information can so also decrease anxiety and the feelings that can lead to a panic state in a panic attack.

8) Awareness of the Inner Workings of Anxiety

An important step in therapy thus to make the person aware of how anxiety affects one's thinking. Individuals from anxiety often focus differently from other individuals. There is often a focus on worst outcomes and strong fears which are caused by it. Underlying this are often strong emotions or conflicts which need to be defended against. The danger and uncertainty are quite frequently inside oneself, rather than on the outside. An individual with a fear of flying may be more afraid of not containing oneself and not being able to leave the plain than anything else. Anxiety is the fear of crashing oneself and the feelings of a dreaded uncertainty about oneself and one's emotional states.

This insight into the inner workings of anxiety is useful because it helps to formulate new strategies in interacting with oneself and with others. A feeling of anxiety has usually the same basic mechanisms in most people, the uncertainty about one's inner world and affective states, the helplessness, the emotions where one has little insight, and which maintain the anxious state, as well as the at least partial disconnect which reduces the insight into the thoughts, sensations, perceptions and feelings which underlie the anxiety. But there are also the individual aspects of what triggers and maintains the anxiety, the own patterns and styles of communicating with oneself and others, which can be scrutinized and experimented with in therapy. Particularly the experimentation can be a helpful tool to create greater awareness for the communication pattern an individual engages in. In the practical context of therapy, questions about irreconcilable thought content or feelings, for example, can be helpful to get the patient to experiment with new perspectives and communication patterns. (Haverkampf, 2010b, 2013, 2017d, 2018b)

Understanding the internal and external communication patterns and styles also provides and understanding for the workings of the anxiety. The reason is that it is not particular content which necessarily leads to anxiety, but how this information is retrieved, viewed and processed. In a neural or any information network all these processes are different version of communicating information from one point to another. Manipulating information also requires communication. If different bundles of information are sent to one point they can be combined, and so on. On a larger scale, there are mechanisms which can malfunction and impede the proper workings of communication, information selection, and so on. In therapy, the focus should be on creating awareness for those points where helpful information cannot happen or can only happen partially. Important for this to work is a good therapist-patient relationship, which id itself the product of awareness for, reflection about and experimentation with communication patterns and flows.

9) Interacting with Oneself

One of the most relevant exchanges one can have is with oneself. But it cannot be separated entirely from one's interactions with one's environment. They both are two sides of one coin. The same rules apply to internal communication as for external communication and vice versa. It is not only necessary to develop awareness for the information coming from inside oneself but also to form patterns that are helpful in the internal communication. As we have seen, anxiety is largely due to a disconnect from oneself and the outside world, as various memories and pieces of information can no longer be seen in the context of other information for the relevance and meaning they truly have, and the lack of cognitive and emotional insight attaches uncertainty not only to them but to one's inner world as a whole.

A therapist can help a patient reconnect with himself or herself in several ways. Using the external communication as a reflection of the internal communication, and vice versa, is a starting point. Patterns where the patient filters information in a certain way or a fear of certain messages may be obvious in patients from anxiety. Apparently high arousal levels without verbal messages that can explain the heightened arousal levels or the attempt to wrap an emotional signal in superficial rationalization of the information may be others. However, awareness of certain patterns is not necessarily a prerequisite of change. Using certain patterns to think about the patient's communicated thoughts and experiences can alter how the patient experiences this information, if the therapist's way is helpful to the patient. The patient integrates the meaningful information gained in a therapeutic setting with the other information contained in the various aspects of memory as well as in the neural network as a whole, which then influences the individual's communication patterns with himself or herself and others. The most effective messages to bring about a change in these communication patterns are those which are about communication itself and which are meaningful in the sense that they can be understood and lead to change. This requires that the therapist makes sure that the information from and about the interaction is understood by the patient. At the same time, both will try to keep the information relevant and helpful. The patient learns in the process to identify what is relevant to him or her, which then has an impact on internal and external ways of communicating.

The process by which one identifies one's own needs, values and aspirations is self-exploration. It means engaging in communication with oneself, being open and receptive to the information one is receiving from one's body and mind, while also being perceptive to one's emotions. The emotions can play an important role in gauging what is 'good' and what is not, because they are the end product of a large amount of information which has been integrated into them over time. So, if one truly feels contentment and satisfaction when engaged in an activity, it may be needed or of special value. Self-exploration is thus not a process of getting lost in one's thought but an active appraisal of the various aspects and activities in life. In a therapeutic setting it helps to ask the patient about how he or she felt in various situations and activities in life. Rather than focusing on the anxiety, greater

focus should be placed on the areas in life which are meaningful and valuable to the patient. When focusing on the anxiety, the main focus is on exploring potential emotional conflicts, which can also include the patient having to do something which goes against the patient's needs, interests, values or aspirations.

Self-exploration has internal and external components, an assessment of internal basic parameters, needs, values and aspirations, as well as an assessment of activities, situations and interactions a patient may engage in. Improvements in internal and external communication can therefore lead to a shift towards following the own needs, values and aspirations, which reduces the level of anxiety.

10) Interacting with Others

Better interactions with others, which reduces anxiety, follows from better interactions with oneself. The reason is that since one cannot know the thoughts or feelings of another person fully, one will always project an element of oneself into the other person. We assume that another person will behave either as they did in the past or in a way that seems to us reasonable, if we judge the other person as reasonable. Thus, to a degree one interacts with oneself when one interacts with another person, while being corrected by the other person about one's assumptions as the exchange progresses. It is thus important to have a good sense of oneself to identify a projection.

Interacting with oneself is also practicing communication, which helps in communicating with others. It is not a substitute for communicating with others, but helps in experimenting with different communication patterns. Also, since there are significant similarities among people on a more basic level, one's own reaction to a thought or feeling can be a good first indication of what another person might feel. This is how art, literature and films can excite multitudes because they touch what is shared by most people.

11) Experiencing the World

To break through the vicious cycle of anxiety, in which emotions like fear and anxiety cause safety thoughts and behaviors, which in turn reinforce feelings of fear, loneliness, sadness, and so forth, it is helpful to focus on identifying what is meaningful and having more of it in life. Communication helps in identifying and finding meaning, either communication with oneself or with others. The exchange of messages is like a learning process in which meaning can be identified, found and accumulated. Through meaningful interactions one accumulates more meaning, more connectedness with oneself and the world and reduces the need for thoughts and behaviors which are triggered by fears, guilt, self-blame and other negative emotions. This also helps against depression and anxiety.

Perceiving more meaning also makes interacting with others and oneself more meaningful. This has a positive effect on one's interaction patterns, how and in which ways one relates to one's environment and exchanges messages with it.

12) Values, Needs and Aspirations

Often, individuals suffering from anxiety or burnout have become uncertain about what is really important to them and the fit between these values and interests and their current life situation. Whether in the professional or romantic realms, following one's needs, values and aspirations has the best chance of maintaining happiness, satisfaction and contentment in the long run. If I value helping people, it is important that I do that to make me feel better in the long-run. Important is to identify those basic parameters which do not change much over time. Often people might be too focused on the short-run at the expense of a greater quality of life in the long-run and potentially higher anxiety levels. Open and rich communication with oneself and the environment can ensure that one gets the correct information about oneself and the world in this respect to make better decisions. Fears of connecting with oneself and the world may interfere with this openness, and it is important to find insight into them in the therapeutic process. Making the fears visible through greater awareness of the own communication patterns, internally and externally, leads to their resolution. This is in turn can then allow the autoregulatory mechanisms of internal and communication to lower the anxiety.

Since values and basic needs remain relatively stable over time, knowing about them can give a patient a greater sense of safety about oneself. Having knowledge of them also helps in interacting with others, partly because one feels more secure about oneself and partly because having a clearer idea about one's needs also helps one to have a clear of others' needs.

13) Meaningful Messages as the Instrument of Change

Communication is the vehicle of change. The instruments are meaningful messages which are generated and received by the people who take part in these interactions. In a therapeutic setting, keeping the mutual flow of information relevant and meaningful brings change in both people who take part in this process.

The therapeutic setting is a microcosm in which the internal world can be played out and the external world be experimented on. An important quality in the therapist is not to take anything that happens in this setting as personal. What happens in the therapeutic setting should be seen as relevant to that specific setting only, which can give the patient a greater sense of safety to bring the internal world out into the setting. By then experimenting and daring new patterns in the setting, the patient develops insight and builds confidence in the communication process with oneself and others. It is the task of the therapist to support the dynamics of this process

through observations, reflection, feedback, and by maintaining healthy boundaries between the therapeutic setting and the outside world. At the same time, the patient will carry more of the insight and skills gained into the therapeutic process into the outside world if it appears helpful and relevant.

V. Other Treatments

Other treatment modalities with insufficient evidence to date can also be considered in treatment-refractory patients. It should be stressed that, given the design and size of the studies, these results should be viewed as preliminary. Risk-benefit ratios should be taken into account. Options include repetitive transcranial magnetic stimulation and aerobic exercise. Repetitive transcranial magnetic stimulation has shown some beneficial effects for panic disorder in several small and open studies (Pigot et al, 2008; Zwanzger et al, 2009). With regard to aerobic exercise, it was found that subsequent to exercise, panic disorder patients had less frequent panic when challenged with carbon dioxide (Esquivel et al, 2008) or cholecystokonin tetrapeptide (CCK-4) compared to controls who had no exercise or only very light exercise (Strohle et al, 2009). In an earlier study aerobic exercise indeed reduced panic symptoms, but later and less effectively than medication (Broocks et al, 1998). Results of a recent randomized controlled trial of aerobic exercise in panic disorder patients were disappointing (Wedekind et al, 2010).

D-cycloserine, a partial agonist of the N-methyl-D-aspartate glutamergic receptor, has recently received attention because it may enhance fear extinction during exposure therapy (Hofmann, 2007). A small (n=31) randomized, double-blind, placebo-controlled trial in which interoceptive exposure was augmented with either low doses of D-cycloserine or placebo showed that panic disorder patients who received D-cycloserine had better outcomes, both at post-treatment, and at 1-month follow-up (Otto et al, 2010).

VI. Conclusion

Panic disorder is a prevalent and disabling disorder that can be treated effectively. However, only a minority of those suffering from panic disorder appear to be adequately treated. The first-line pharmacotherapy for panic disorder is SSRIs with the addition of the SNRI venlafaxine. Several strategies have been described on the psychopharmacological side, including switching and augmentation.

Psychotherapy is more targeted at stabilization and maintenance of remission over the long-term. When working with patients suffering from anxiety and panic attacks, a communication- and insight focused approach seem particularly helpful. Empathy and an understanding and supportive approach are very valuable, as in all other mental health and medical conditions.

Statement on Conflicts of Interest

The author reports no conflicts of interest.

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