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# Individual negative symptoms and domains – Relevance for assessment, pathomechanisms and treatment

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ABSTRACT

The negative symptoms of schizophrenia can be divided into two domains. Avolition/apathy includes the individual symptoms of avolition, asociality and anhedonia. Diminished expression includes blunted affect and alogia. Until now, causes and treatment of negative symptoms have remained a major challenge, which is partially related to the focus on negative symptoms as a broad entity. Here, we propose that negative symptoms may become more tractable when the different domains and individual symptoms are taken into account. There is now increasing evidence that the relationship with clinical variables - in particular outcome - differs between the domains of avolition/apathy and diminished expression. Regarding models of negative symptom formation, those relevant to avolition/apathy are now converging on processes underlying goal-directed behavior and dysfunctions of the reward system. In contrast, models of the diminished expression domains are only beginning to emerge. The aim of this article is to review the specific clinical, behavioral and neural correlates of individual symptoms and domains as a better understanding of these areas may facilitate specific treatment approaches.


## 1. The structure of negative symptoms

According to the NIMH MATRICS consensus statement, negative symptoms include blunted affect, alogia, asociality, anhedonia and avolition (see Fig. 1) (Kirkpatrick et al., 2006). There is now a broad consensus that these negative symptoms can be grouped into two domains – avolition/apathy and diminished expression (see Fig. 1) (Blanchard and Cohen, 2006; Kirkpatrick, 2014; Messinger et al., 2011). The avolition/apathy domain consists of avolition, asociality and anhedonia. Several other terms have been used for this domain, e.g. 'experiential' (Park et al., 2012) and 'motivation/pleasure' domain (Kring et al., 2013; Strauss et al., 2012a), but we employ the terms avolition/apathy in line with Messinger et al. (2011) and Kirkpatrick (2014). The diminished expression domain consists of blunted affect and alogia. While this two factor solution already emerged from factor analytic studies of the Scale for the Assessment of Negative Symptoms (SANS), two newly developed scales for assessment of negative symptoms, the Clinical Assessment Interview for Negative Symptoms (CAINS) and Brief Negative Symptom Scale (BNSS), have been explicitly designed to reflect the two-domain structure of negative symptoms (Kring et al., 2013; Strauss et al., 2012a). In addition, scales specifically assessing one domain have been used, for example the Apathy Evaluation Scale (AES) (Faerden et al., 2008).

It is not yet clear whether the individual negative symptoms (avolition, asociality, anhedonia, blunted affect, alogia) can be fully reduced to these two domains. For example, although avolition and asociality both load on the factor avolition/apathy, there remain conceptual differences between the two symptoms. Regarding the cognitive and neural basis it is conceivable that there are common mechanisms contributing to all individual symptoms in the avolition/apathy domain, for example reward system dysfunction. However, there may also be mechanisms that are specific to one individual symptom, for example an impairment of social cognition would only be relevant for asociality. Therefore, in this review we address individual negative symptoms in addition to the two domains avolition/apathy and diminished expression, although the differentiation into the two domains currently has the strongest support.

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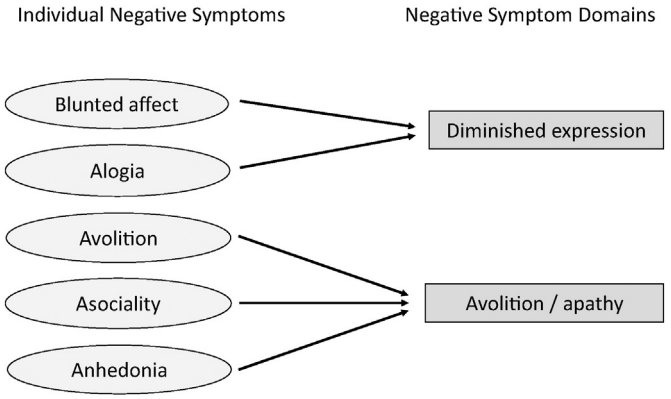


**Fig. 1.** Individual negative symptoms cluster in the domains diminished expression and avolition/apathy.

This structure of negative symptoms is of great interest for several reasons. Firstly, domains and symptoms may be differentially associated with clinical variables, for example outcome. Secondly, domains and symptoms may have different behavioral and neural correlates. Thirdly, the response to treatments may differ across dimensions and symptoms. Thus, the aim of the present review was to delineate the psychopathology of the domains of avolition/apathy and diminished expression at an individual symptom level and to explore current models of symptom formation and their empirical support in behavioral and neuroimaging studies.

## 2. The avolition/apathy domain

We employ the term avolition/apathy to designate the domain consisting of the individual symptoms avolition, asociality and anhedonia. Thus, the avolition/apathy domain covers a broad range of symptoms, which include a reduction in motivation and goal-directed behavior as well as a diminution in the experience of pleasure (Foussias and Remington, 2010; Messinger et al., 2011). The term avolition has been used to designate both the domain avolition/apathy and the individual symptom described in the following section.

### 2.1. Avolition

Andreasen defined avolition as a characteristic lack of energy, drive and interest (Andreasen, 1982) in activities such as work/school, recreation and self-care. In the SANS, most of the items used for avolition focus on objective reduction in activities and less on motivation to engage in these activities. With the newer scales, BNSS and CAINS, the emphasis has shifted to include subjective motivation more strongly (Kirkpatrick et al., 2011; Kring et al., 2013). While the lack of motivation generally also affects social activities, these are rated separately as asociality or decreased motivation in social situations. Importantly, avolition is the negative symptom most strongly associated with subjective distress (Selten et al., 2000).

Although interview-based measures remain the gold standard for the assessment of avolition, the use of more objective measures that keep track of actual patient activity within a defined time-period, particularly in an outpatient setting has been challenging (Tremeau et al., 2012). A systematic written documentation of activities by the patient and the use of actigraphy, i.e. sensor-based continuous measurement of gross motor activity, have shown promise (Jolley et al., 2006; Walther et al., 2015). An important avenue for further research may be ecological momentary assessment, which allows 'online' documentation of activity and subjective experience (Oorschot et al., 2013). However, thus far this approach has not to our knowledge been applied to the study of avolition.

Regarding the cognitive and neural basis of avolition, most studies have not addressed the individual symptom of avolition, but rather the whole avolition/apathy domain including asociality and anhedonia. Therefore, they will be discussed in the sections on cognitive and neural correlates of the avolition/apathy domain below.

### 2.2. Asociality

Asociality is defined as withdrawal from social contact that derives from indifference or lack of desire to have social contact (Kirkpatrick et al., 2011). As social withdrawal can be caused by many different factors, recent negative symptom scales do not define asociality in purely behavioral terms, but require a rating of both behavior and motivation for social contact (Kirkpatrick et al., 2011; Kring et al., 2013).

Asociality is considered to be a core feature of schizophrenia that contributes to poor psychosocial functioning and poor outcomes in general (Marchesi et al., 2015). Furthermore, social withdrawal is a childhood risk factor for later schizophrenia (Matheson et al., 2013). Asociality also occurs in other disorders such as schizoid personality disorder and autism (Couture et al., 2010; Kastner et al., 2015). The degree of shared phenomenology and mechanisms across disorders remains a field of intensive study.

There are only limited studies investigating the processes and neural mechanisms of asociality in schizophrenia. Most research has addressed asociality as social amotivation and has therefore included asociality with other symptoms in the avolition/apathy domain as will be discussed below (Liemburg et al., 2013; Messinger et al., 2011). However, two aspects specific to asociality deserve mention. Firstly, a link between asociality and social cognition has been suggested, but the extent and nature of this association remains a matter of ongoing research (Millan et al., 2014). Secondly, a number of recent studies have suggested that a reduction in oxytocin levels may contribute to asociality in patients with schizophrenia, which would have direct implications for treatment (Jobst et al., 2014; Strauss et al., 2015).

### 2.3. Anhedonia

Anhedonia can be defined as a diminished capacity to experience pleasant emotions (Horan et al., 2006). This general definition has not changed over the last decades and anhedonia has long been considered to be a core symptom of both depression and schizophrenia (Meehl, 1975). More recently, a distinction between consummatory and anticipatory anhedonia has been made (Gard et al., 2007). This is of great potential relevance as anticipatory anhedonia seems to be particularly affected in individuals at risk for psychosis, with first-episode psychosis and with schizophrenia (Gard et al., 2007; Mote et al., 2014; Schlosser et al., 2014), although there are also discrepant findings (Strauss et al., 2011b). In contrast to these findings which stem from self-rating scales, the two constructs - anticipatory and consummatory anhedonia - do not seem to separate in factor analytic studies of interview-based scales (Kring et al., 2013; Strauss et al., 2012a).

A common topic to research on anhedonia in schizophrenia is the "emotion paradox" (Strauss, 2013). Patients with schizophrenia show intact emotional response when measured directly in response to positive stimuli, but show anhedonic responses when reporting past or future experiences (Kring and Moran, 2008). A recent account explains anhedonia in terms of impaired accessibility of non-current emotional states (Strauss and Gold, 2012). Other authors have argued that the traditional definition of anhedonia as diminished experience of pleasure should be revised in favour of a definition including the motivational properties of rewards (Romer Thomsen et al., 2015).

In line with behavioral studies indicating intact consummatory or "in-the-moment" pleasure in patients with schizophrenia, neural activity during viewing affective images was not found to be associated with anhedonia in one functional magnetic resonance imaging study (Ursu et al., 2011). However, after a delay, participants were asked to rate the

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valence and the emotion they experienced when viewing the images. Activity in the orbitofrontal cortex (OFC) and dorsolateral prefrontal cortex (DLPFC) during the delay was negatively correlated with the severity of the anhedonia. In contrast, Dowd and Barch found attenuated activation in response to positive stimuli in patients in the right ventral striatum and left putamen compared to healthy controls (Dowd and Barch, 2010). This attenuated activation was correlated with higher physical anhedonia in the patients.

### 2.4. Cognitive models of the avolition/apathy domain

Current explanatory models of the avolition/apathy domain focus strongly on processes relevant to motivation (Foussias et al., 2015; Strauss et al., 2014). Although these processes are most directly linked to the individual symptom of avolition, it is important to note that asociality can be interpreted as social amotivation. Since the in-the-moment experience of pleasure seems to be intact in patients with schizophrenia, the focus with respect to anhedonia has shifted to the anticipation of pleasure, which is also closely linked to motivation (Foussias and Remington, 2010; Kring and Moran, 2008). It has been suggested that reduced motivation underlies not only symptoms of the avolition/apathy dimension but all negative symptoms including diminished expression (Foussias and Remington, 2010). However, since the empirical evidence for a causal role of poor motivation for diminished expression is limited, we focus on the relationship between motivational processes and avolition/apathy.

Research on motivational impairment has been strongly influenced by animal research on reward processing, neuroeconomics and cognitive neuroscience (Barch and Dowd, 2010; Strauss et al., 2014). A deficit in the ability to predict and learn from rewards contributes to amotivation in patients with schizophrenia (Gold et al., 2012; Waltz et al., 2007). This deficit might best be explained by an impairment of value representations in the OFC, which provide the basis for the calculation of prediction errors. More recently, the computation of action values based on the available rewards and the required effort has received increasing interest (Gold et al., 2015). Several studies have suggested that patients with schizophrenia are less willing to invest effort to obtain a reward and that this shift in their decision pattern is related to the avolition/apathy dimension (Fervaha et al., 2013; Hartmann et al., 2015a). However, given the divergent findings (Gold et al., 2013; Horan et al., 2015), replications are needed. Additionally, a recent study showed that exploratory behavior is reduced in patients with avolition/apathy (Strauss et al., 2011a).

Another line of research has addressed potential psychological mechanisms that could contribute to motivational impairments in patients with schizophrenia. Grant and Beck have suggested a model according to which neurocognitive impairment and negative experiences lead to negative expectations about one's ability to successfully engage in goal-directed tasks (Grant and Beck, 2009). There is now increasing evidence that these defeatist beliefs and negative expectations contribute in particular to the avolition/apathy or experiential domain (Couture et al., 2011; Quinlan et al., 2014). Another important aspect is the potential role of stigma and stigma resistance for motivation and pleasure (Campellone et al., 2014). These models form the basis for more recently developed cognitive behavioral interventions (Grant et al., 2012; Staring et al., 2013).

Finally, it has been suggested that an impairment in cognitive processes for the elaboration of plans for action can contribute to avolition/apathy (Levy and Dubois, 2006). In line, with this hypothesis apathy has been found to be associated with executive functions in a large sample of patients with first-episode psychosis (Faerden et al., 2009). However, the effect of this association was weaker in other studies (Hartmann-Riemer et al., 2015; Kring et al., 2013). Therefore, it has been suggested that cognitive processes have to be addressed more specifically in relation to action planning. For example, Hartmann and colleagues demonstrated that apathetic patients generate fewer options for action in ill-structured situations (Hartmann et al., 2015b). Overall, it would be important to investigate the relationship between cognitive domains and negative symptom domains in more detail.

### 2.5. Neural correlates of the avolition/apathy domain

A limited number of imaging studies have investigated underlying structural correlates within the avolition/apathy domain in patients with schizophrenia. Apathy has been related to smaller frontal lobe volumes in patients with chronic schizophrenia (Roth et al., 2004), and thinner left OFC and anterior cingulate cortex (ACC) in first-episode psychosis patients (Morch-Johnsen et al., 2015). Consistent with this observation altered structural connectivity between medial OFC and rostral ACC was shown to be associated with higher SANS scores of avolition-apathy and anhedonia-asociality (Ohtani et al., 2014; Ohtani et al., 2015). In addition, reduced white matter volume and fractional anisotropy in other brain regions has been associated with items from the avolition/apathy domain (Asami et al., 2014; Chuang et al., 2014), but these findings await replication.

Functional magnetic resonance (fMRI) studies have tried to elucidate motivational impairment in patients with schizophrenia by using reward anticipation tasks. An association between ventral striatal activation and the whole range of negative symptoms was mainly observed in patients who were medication free or on typical antipsychotics (Juckel et al., 2006; Schlagenhauf et al., 2008). However, when relating ventral striatal activation more specifically to the avolition/apathy domain, an association was also found in patients treated with atypical antipsychotics (Kirschner et al., 2015; Simon et al., 2010; Waltz et al., 2010). In addition, the study by Kirschner and colleagues showed that ventral striatal activation was not associated with diminished expression, which suggests at least some degree of specificity. Finally, other striatal regions may contribute to the association with avolition/apathy. For example, Mucci and colleagues found dorsal caudate activity during reward anticipation to be associated with real-life motivation and avolition, but not with anhedonia (Mucci et al., 2015). It is important to note that the studies reviewed here used overlapping, but not identical definitions of the avolition/apathy domain. However, all of the studies included the individual symptoms avolition and asociality in their definition (Kirschner et al., 2015; Mucci et al., 2015; Simon et al., 2010; Waltz et al., 2010).

## 3. The diminished expression domain

Expression deficits can be defined as a decrease in the outward expression of emotion and speech (Horan et al., 2011; Kirkpatrick et al., 2011). As described earlier, blunted affect and alogia are the two individual symptoms within the diminished expression domain.

### 3.1. Blunted affect

Blunted affect or affective flattening has been referred to as 'a decrease in the outward expression of emotion' (Kirkpatrick et al., 2011). This manifests itself as a characteristic impoverishment of emotional expression, reactivity and feeling (Andreasen, 1984). Blunted affect has been consistently included in negative symptom scales, such as the SANS, CAINS and BNSS, and is evaluated by measuring constructs such as facial expression, vocal expression and expressive gestures (Kilian et al., 2015). The assessment of blunted affect traditionally relies on the "objective" assessment by an observer rather than the subjective experience of decreased emotional range. Furthermore, some items included in the SANS, such as decreased spontaneous movements and poor eye contact have been omitted from newer scales (Horan et al., 2011; Strauss et al., 2012b).

Similarly to other negative symptoms (Savill et al., 2015), prevalence of flat affect has been shown to fluctuate over the longer term (Evensen et al., 2012). Research has suggested that flat affect is more common in

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men with schizophrenia, and is associated with both poorer premorbid adjustment and worse outcomes (Gur et al., 2006). Although flat affect is associated with poor social functioning (Evensen et al., 2012), there is also evidence that flat affect is independent of social skills (Salem and Kring, 1999).

### 3.2. Alogia

Alogia can be defined as a decrease in the outward expression of speech (Horan et al., 2011). It has also been described as a general term to refer to the impoverished thinking and cognition that often occurs in schizophrenia (Andreasen, 1984), but current concepts restrict the term to speech. Alogia can be measured by evaluating both the quantity and spontaneous elaboration of speech. The SANS items 'blocking' and 'increased latency of response' have not been included in CAINS and BNSS.

Some investigators have classified alogia symptoms under 'negative thought disorder' (poverty of speech and poverty of content of speech), which has been shown to be a poor predictor of outcome (Wilcox et al., 2012). Previous studies have reported alogia items to load onto a disorganization or thought disorder domain, particularly for 'poverty of content of speech' (Miller et al., 1993) and 'blocking' items (Peralta and Cuesta, 1995), however most studies include alogia as part of the negative syndrome (Smith et al., 1998).

Acoustic analysis is also used to measure speech variables related to alogia, and research has suggested that vocal expressive deficits may be present across several psychiatric diagnoses as well as schizophrenia (Cohen et al., 2012b). However, our understanding of alogia and vocal expression remains limited and it is possible that only certain aspects of vocal expression are affected in schizophrenia (Cohen et al., 2014b).

### 3.3. Cognitive models of the diminished expression domain

In contrast to avolition/apathy, there is a lack of models for the diminished expression domain. However, tentative models have been constructed separately for blunted affect and alogia.

Blunted affect has been considered to be associated with deficits in emotion perception (Gur et al., 2006; Lepage et al., 2011), which could lead to an inability to adequately reciprocate in social interactions. Indeed a poorer performance on emotion processing tasks for identification of emotions has been observed for individuals with negative symptoms (Kohler et al., 2010) and flat affect in particular (Gur et al., 2006). However, other studies have not found a deficit in emotion perception and processing to be associated with diminished expression (Strauss et al., 2013). Accordingly, the suggestion that flat affect is a purely emotional deficit has long been questioned (Blanchard et al., 1994), and some studies indicate that flat affect may be more related to a deficiency of motor expression than emotional impairment (Alpert et al., 2000; Kring and Moran, 2008).

Regarding mechanisms underlying alogia, Cohen has developed the cognitive resource limitation model (Cohen et al., 2014a; Cohen et al., 2012a). He argues that speech production in social situations places high demands on multiple cognitive processes. If cognitive resources are limited, patients will reduce their speech production. In line with this notion, alogia has been associated with cognitive deficits affecting controlled retrieval (Docherty et al., 2011), semantic memory (Sumiyoshi et al., 2005) and poor verbal fluency (Joyce et al., 1996). It is also of note that negative correlations of general cognitive ability tend to be stronger with diminished expression than with avolition/apathy (Galderisi et al., 2014; Hartmann-Riemer et al., in press), which could also support the cognitive resource limitation model.

Thus, in summary, although alogia and flat affect load consistently on the same factor in psychometric assessments (Blanchard and Cohen, 2006; Kring et al., 2013; Strauss et al., 2012a), there is currently no model or behavioral evidence for a common mechanism underlying the diminished expression domain. Work on such a model could be essential for progressing research on this domain.

### 3.4. Neural correlates of the diminished expression domain

In contrast with avolition/apathy, no consistent findings of a specific association of diminished expression with structural brain changes have emerged (Ballmaier et al., 2008; Bijanki et al., 2015; Makris et al., 2010).

Several investigators have used functional MRI (fMRI) to study a model of emotional processing deficits as the neurofunctional basis of blunted affect. Lepage et al. investigated the processing of sad, happy and neutral faces, which activated a distributed network involving prefrontal areas, amygdala, cingulate cortex and cuneus (Lepage et al., 2011). Patients with flat affect showed reduced activation of the left amygdala and the parahippocampal gyrus. This finding was recently supported by Rahm et al., who observed a significant negative correlation between emotional blunting and neural activation in the left amygdala during processing of positive affect (Rahm et al., 2015). Thus, the findings from these two studies support the notion that amygdala dysfunction plays a key role in the pathophysiology of blunted affect as suggested by Aleman and Kahn (Aleman and Kahn, 2005).

Stip et al. focused on the role of the prefrontal cortex in emotion processing (Stip et al., 2005). They examined ventrolateral prefrontal cortex (VLPFC) activation in response to the passive viewing of sad and neutral social situations. Hypoactivation during emotion processing was observed in VLPFC in the blunted affect group. This group also showed dysfunctional circuitry throughout the brain characterized by hypo- and hyperactivation. It was thought that the dysfunction of these distributed circuits impairs emotion processing and prevents efficient processing input as well as output in the brain, thereby leading to blunted affect. An important role in emotional expression has also been attributed to the mirror neuron system. In a study by Lee and colleagues the severity of affective flattening showed a significant negative correlation with signal activities in the mirror neuron system, including the premotor cortex, motor cortex, and inferior parietal lobule (Lee et al., 2014). Overall, different aspects of neural emotion processing may be associated with blunted affect, but a consistent picture has yet to emerge.

In contrast to the functional imaging tasks investigating an emotional processing deficit model of blunted affect, the cognitive resource limitation model for alogia has received little attention in the neuroimaging literature. In a recent study, Hager and colleagues showed in a reward-cognition interaction task, that activation of the rostral ACC is inversely related to diminished expression, which suggests an inefficient additional recruitment of cognitive resources when a reward is at stake (Hager et al., 2015). However, for a more detailed analysis of the model, functional neuroimaging tasks involving speech production will be needed.

## 4. Differences between diminished expression and avolition/apathy domains

Relatively few studies have directly compared the clinical characteristics between the two domains avolition/apathy and diminished expression. There is evidence that the avolition/apathy domain has higher prevalence than the expressivity domain in the early phases of psychosis (Lyne et al., 2015b). Diminished expression symptoms, in particular affective flattening, have been shown to be more persistent across time (Kelley et al., 2008), and may predict the presence of persistent as opposed to transitory negative symptoms (Galderisi et al., 2013; Malla et al., 2004). Some have considered expressivity symptoms as the 'core' negative symptoms in schizophrenia (Barnes et al., 2008), and one study found that expressivity subscales were more specific to schizophrenia than avolition/apathy subscales (Fennig et al., 1996).

Evidence linking domains of negative symptoms with functional outcomes is stronger for avolition/apathy than for diminished

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expression (Sayers et al., 1996; Strauss et al., 2013). This may reflect overlap between the assessment of avolition/apathy and functioning, so newer scales have aimed at distinguishing the two (Blanchard et al., 2011). The two domains also show different relationships with the duration of untreated psychosis (DUP). Early in the illness, DUP seems to be associated with avolition/apathy subscales, but not with expressivity subscales (Malla et al., 2002). The same study found a significant association between the duration of the psychosis prodrome and expressivity domain subscales, but not avolition/apathy subscales. Another study reported a stronger relationship between the duration of active psychosis and expressivity domain than the avolition/apathy domain at two year follow-up (Lyne et al., 2015a).

Research comparing the response to treatment for each of these domains is in its infancy and few clinical trials have so far reported separate outcomes for avolition/apathy and diminished expression. Some preliminary evidence indicates that there may be differences in outcome between negative symptom domains from pharmacological (Buchanan et al., 2008; Umbricht et al., 2014) and psychotherapeutic trials (Grant et al., 2012).

## 5. Conclusion

Recently developed negative symptom scales have refined the measurement of negative symptoms, which should improve our understanding of negative symptoms in future studies. While the psychometric evidence currently supports a two domain model of negative symptoms, further studies of individual negative symptoms are needed to improve psychopathological assessment and to investigate more specific etiological models and psychobiological correlates. A critical issue in the research reviewed is the heterogeneous definition of negative symptoms and domains.

There is increasing evidence that the domains of avolition/apathy and diminished expression relate to different clinical aspects of schizophrenia. Whether these domains have separate aetiologies requiring different treatment strategies merits further investigation, but findings from behavioral and neuroimaging studies support distinct underlying mechanisms. Although it may be too early to develop specific treatment approaches for these domains, an important starting point would be to report results for avolition/apathy and diminished expression separately in all studies, in particular clinical trials.

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### Contributors

SK, JL and AF developed the conceptual outline for the review. All authors contributed to the literature search and the writing of the manuscript. All authors have approved the final manuscript.

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