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# Novel Modalities for Assessment and Intervention in Youth Mental Health

## Digital Interventions and Omega-3 Fatty Acids

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**Abstract**

Extant interventions and services for young people with mental ill-health and their families have significant limitations, including poor access to services, relapse prevention, social recovery, research translation, and family support as well as limited effectiveness and significant adverse events of pharmacological interventions. Based on research literature and the authors' work in the field, this chapter reviews three avenues for progress: novel digital, family, and transdiagnostic biomarker-guided interventions.

Main findings and conclusions: Despite their potential and consistent evidence supporting their effectiveness, digital interventions have not been integrated into youth mental health services. Integration of digital interventions into mainstream services is likely to create a new paradigm, driven by ongoing innovation and rapid evaluation and clinical implementation. Family interventions need to move away from a narrow focus on psychotic disorders, patient symptoms, and relapse to include overlooked populations, transdiagnostic processes, family burden, and the mental and physical health of families. Finally, transdiagnostic prevention and treatment of severe psychiatric disorders is a promising avenue for reducing the burden, mortality gap, and adverse effects of current medications. Supplementation of n3PUFA via fish oil is proposed as a prototype of a transdiagnostic, benign, biomarker-guided intervention.

From "Youth Mental Health: A Paradigm for Prevention and Early Intervention," edited by Peter J. Uhlhaas and Stephen J. Wood. Strüngmann Forum Reports, vol. 28, Julia R. Lupp, series editor. Cambridge, MA: MIT Press. ISBN 978-0-262-04397-7

## Key Limitations of Current Interventions and Mental Health Services for Youth

The past 25 years has seen significant progress in interventions and models of care designed to improve the clinical symptoms of young people with mental ill-health and to support their families. Early intervention is now seen as the most promising and evidence-based approach to improve the long-term outcomes of mental disorders (McGorry et al. 2008a). Specialist early intervention services for psychosis originated in the early 1990s, with a focus on reducing treatment delays, providing youth-friendly, phase-specific support, and preventing the development of long-term functional and social disability (McGorry et al. 2008a). Over the past two decades, several randomized control trials (RCTs) conducted across countries and mental health systems have demonstrated that these services improve psychotic symptoms, reduce relapse rates, foster patient satisfaction, and result in tangible economic benefits (Alvarez-Jimenez et al. 2011; Bird et al. 2010; Craig et al. 2004; Melle et al. 2004; Petersen et al. 2005). The success of the reforms supporting early intervention for psychosis has led to the extension of this model to other mental health conditions, including the development of youth mental health services for both subthreshold clinical conditions as well as severe mental health disorders, such as borderline personality disorder or complex depression (Chanen and McCutcheon 2013; Rice et al. 2017). Despite these advances, current youth mental health interventions and services have major limitations:

- *Relapse prevention failure*: Youth mental health services are not equipped to effectively prevent relapse. The result is that up to 80% of young people with depression or psychosis will suffer repeated recurrences after initial treatment response, thereby increasing the risk of long-term disability (Alvarez-Jimenez et al. 2012; Kennard et al. 2006).
- *Social recovery failure*: Existing interventions have limited impact on key domains of social recovery, such as social connectedness, employment, or well-being (Horan et al. 2006). Not only are these deficits the most disabling and costly aspect of mental illness, achieving social recovery is the most valued goal for young people and their families.
- *Innovation failure*: The variety of evidence-based treatments available to young people has remained largely unchanged over the past four decades, and has been limited to psychotherapies or psychotropic medications. No specific guidelines on the indications for psychological treatment versus medication have been provided for most psychiatric disorders. While public views tend to favor the psychotherapies as first-line interventions, one problem with this approach is workforce capacity constraints, leading to failure of access to services.
- *Access failure*: Seven out of ten young people and the majority of their families do not have access to evidence-based interventions (Reavley et al. 2010). Even when they receive treatment, many discontinue

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treatment too soon, and they have no access to personalized support when they need it.

- *Research translation failure*: Research translation is painfully slow, with up to 17 years of delay between treatment innovations and their dissemination across mental health services (Mohr et al. 2018).

## Digital Interventions and Youth Mental Health Reform: Can Technology Drive the Next Transformation in the Field?

### The Promise and Unmet Expectations of the First Generation of Digital Interventions

One avenue to address the limitations of current interventions and youth mental health services is to harness digital technologies to increase their accessibility, attractiveness, cost-effectiveness, and impact. Digital mental health interventions include devices and programs that harness digital technology to foster improved mental health outcomes (Michie et al. 2017). This can include computer-based interventions (with or without online access), online-based interventions (e.g., self-guided online programs, online interventions including therapist support), mental health mobile applications (e.g., interventions delivered by mobile applications, such as ecological momentary interventions), or virtual reality-based interventions. The most widely researched type of digital mental health interventions are online-based interventions. Indeed, there is strong evidence for the effectiveness of online interventions in both adults and young people, particularly for high prevalence mental health disorders such as depression and anxiety disorders, from over 100 clinical trials (Richards and Richardson 2012). Encouraged by this evidence, mental health-care systems have attempted to integrate digital technologies, as in the Australian national E-mental health strategy, which recommends integrating online support with youth mental health services (Australian Government Department of Health and Ageing 2012). Yet, around the world, integration of digitally enabled support with current models of care has not been implemented, leading to fragmentation of online support and youth mental health services. Despite being evidence-based, online interventions are rarely taken up by young people or clinicians in the real world (Mohr et al. 2018). Concurrently, there has been an explosion of mobile applications claiming to improve well-being and to reduce depression or anxiety, yet very few have quality evidence to support their safety or effectiveness. Consequently, while young people have more ready access to potential supports than ever before, they have no means to determine their quality. Conversely, when they do access mental health services and face-to-face interventions, these are not complemented by personalized and engaging digitally based support to enhance their generalizability and impact.

Further limitations that have significantly hampered the promise and impact of existing online supports include very high attrition rates, especially among

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online interventions without human support, usually after only one or two sessions, thereby limiting their ability to address relapse prevention (Gilbody et al. 2015). Also, online support has primarily focused on clinical symptoms, with little attention paid to social, educational, employment, and other functional outcomes. Finally, online interventions have typically targeted mild to moderately high-prevalence disorders; very few have addressed severe mental health conditions (e.g., psychosis, bipolar disorder, or borderline personality disorder).

Drawing on our work on online interventions in youth mental health, we propose that for digital interventions to be able to deliver on their promise to revolutionize mental health services, the new generation of technology-driven interventions needs to harness contemporary methodologies and technologies to promote sustained engagement, so that long-term outcomes, such as relapse prevention, can be addressed. Such interventions will need to draw upon novel as well as robust psychological models that focus on well-being and social functioning. Moreover, they will need to be designed from the outset to be integrated with real-world mental health services and settings, at all stages of treatment, and they will need to integrate a new blend of multidisciplinary expertise, including that of young people and families.

## Toward Long-Term Engagement: The Science of Developing Online Interventions in Youth Mental Health

Commercial online social media platforms such as Facebook, Instagram, and Snapchat have a well-demonstrated capacity to engage young users, even to the point of becoming addictive. Driven by the "attention economy," whereby harvesting attention has become their key metric of business success, these platforms run thousands of tests with their users and take advantage of known social and cognitive biases to devise (disguised) strategies that capture users' attention. The results of this approach are remarkable: 50% of 18- to 24-year-olds go on Facebook when they wake up, 90% of young people use online social media daily, and young people under the age of 25 use Snapchat 20 times for over 30 minutes every day (Hadad 2015; Rideout 2015; Smith 2016). Unfortunately, accumulating evidence shows that using online social media platforms can have detrimental effects upon youth. These include high rates (around 23%) of cyberbullying (which is strongly associated with depression and is often suffered in silence), increased anxiety, negative body image and, paradoxically, an increased perceived social isolation among those feeling lonely (Rideout 2015). Purely harvesting attention, as it turns out, can have severe adverse consequences for young people. On the other hand, most evidence-based online interventions have been designed to replicate traditional, effective, face-to-face therapeutic principles (e.g., cognitive behavioral therapy), with little attention to design choices aimed at promoting sustained engagement. The result is that these interventions have traditionally been plagued by disappointing engagement rates over the longer term.

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Building on the useful knowledge that digital interventions can deliver effective psychological support, we need to advance the science of developing digital interventions in youth mental health. The design and development process of new digital interventions is critical to ensure quality interventions that are safe, engaging, and effective. The field needs to fully embrace and adapt best practices in software design as well as persuasive methods and strategies. As scientists and clinicians, we need to promote the "well-being economy" as an alternative model, where supporting meaningful and lasting benefits is the end goal. As such, the new generation of technology-based interventions needs to harness the appeal and therapeutic potential of online social media technologies, while engineering digital interventions that enable meaningful and positive relationships and foster well-being in an ethical, safe, and transparent manner. Advancing the well-being economy will require a new blend of multidisciplinary expertise, including clinical psychologists, creative writers, software developers, artists, experts in human computer interaction, game developers, and experts in machine learning who work in partnership with end users.

## Developing New Methodologies to Evaluate the Effects of Digital Interventions

Rapid development of online technologies has outpaced the timeline of conventional RCTs. This is, however, not the case for RCTs that evaluate mobile health interventions (which can recruit from a global pool of potential participants, thereby conducting fast and efficient RCTs) in high prevalence conditions, such as depression and anxiety. This limitation applies to studies conducted in traditional clinical services that recruit specific populations (e.g., young people with psychosis or at clinical risk of developing psychosis) (Alvarez-Jimenez et al. 2018) with prolonged follow-up periods (e.g., 18 months or longer). In the latter case, studies can take up to five years to be completed (Alvarez-Jimenez et al. 2019). This results in evaluations of interventions that are obsolete by the time trial results become available, preventing real-world implementation.

Novel research frameworks put forward solutions to this issue, balancing the need for ongoing technological improvements while maintaining the internal validity of the interventions being tested (Mohr et al. 2015). In this way, the core elements and theoretical principles of a technology-based intervention can be operationalized and remain consistent during the evaluation process, while allowing for ongoing quality improvements in functionality, thereby maintaining technological currency (Mohr et al. 2015). That said, rigorous methodologies need to be developed and applied to reliably measure the intervention principles and their consistent implementation throughout the trial.

An additional alternative to conducting traditional, slow, and expensive clinical trials of digital interventions in the context of clinical services (which

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lack a direct pathway to clinical implementation) is to make youth mental health services digitally enabled by integrating digital interventions designed to enhance their impact. By providing technology-enabled support to all young people using these services—potentially hundreds of thousands—we could then conduct rigorous, fast, and efficient RCTs of progressive updates, releases, and new digital tools delivered as part of the service. Crucially, the results of these RCTs can be readily implemented in the clinical service by making the new intervention available to all service users (vs. the up to 17-year delay in current research translation).

## Integrating Digital Interventions and Assessments into Youth Mental Health Services

Rather than evaluating digital interventions where real-world implementation and integration is an "after the fact" procedure, digital interventions need to be designed from the outset to be integrated within youth mental health services. This implementation needs to occur at all stages of treatment, including help-seeking, blended face-to-face online support, as well as digital interventions to prevent relapse and maintain the hard-won gains of face-to-face interventions. To create effective interventions that address critical issues for young people and their families and clinical services, all relevant stakeholders, including clinicians, end users, and administrators, need to be part of the design process. Importantly, new business models need to be developed that account for the need for ongoing evaluation and regular technological improvements, while also meeting the expectations of young people that they receive modern, constantly evolving, and effective support.

The integration of digital interventions and assessments into current models of care offers fascinating new possibilities. Rather than being an "add-on" or even a replacement for effective face-to-face interventions, digital technologies can be used to create a new model of synergistic care that breaks down the perceived online/offline divide. For example, at Orygen, we have developed a new blended model of care entitled Moderated Online Social Therapy + (MOST+) through which young people can access support from other young people at all times, day or night, as well as peer supporters and moderators between sessions. In addition, MOST+ includes a comprehensive array of high-quality, interactive, evidence-based interventions that can be recommended by the clinician, selected by the young person, or automatically suggested by the system, based on individual preferences and needs. The clinicians and young people are able to schedule action plans and homework based on team and geographic location. Importantly, the system can harness real-time assessment methodologies, such as ecological momentary assessments (Shiffman et al. 2008) or digital phenotyping enabled by a smartphone application (Insel 2017), to capture the changing needs and emotions of young people *in vivo*. Coupled with novel data science tools, such as artificial

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intelligence (D'Alfonso et al. 2017) and machine learning (Torous et al. 2018), this information can subsequently be used to identify patterns of behavior and emotions, to evaluate progress, and to tailor therapeutic interventions in real time via ecological momentary interventions (Heron and Smyth 2010; Myin-Germeys et al. 2016).

## Priorities for Family Assessment and Intervention

The onset of severe mental ill-health in a young person often marks the start of a major crisis in the lives of their families. In the process of caring for their young relative, family members often suffer high levels of stress, burnout, and depression (Onwumere et al. 2011, 2018), and exposure to violence is not an uncommon result (Onwumere et al. 2014). Since mental health disorders often emerge when families expect their young person to become increasingly independent, it is not surprising that the young person experiences a sense of grief after initial diagnosis—a sense of loss or separation from family, friends, or other carers[1] (Patterson et al. 2005; Tennakoon et al. 2000).

Despite decades of robust research on the efficacy of family interventions in severe mental health disorders and clinical guidelines recommending their deployment (most notably for schizophrenia), access to effective interventions remains a lottery for most families (Bucci et al. 2016). In youth mental health, the evidence base for family intervention is less well established. Mounting evidence indicates, however, that it is effective in reducing the risk of both relapse and family/carer distress (Claxton et al. 2017).

In the context of this promising evidence and high level of unmet need, we explore key priorities for family assessment and interventions in youth mental health. Focusing on recent and potential innovations in the assessment of family needs and the delivery of family interventions to address access logjams, we identify critical targets for family interventions that have been overlooked and note specific populations of families whose needs have been largely ignored by researchers. Finally, we consider the implications of changing family structures and environments for the future of family-level assessment and interventions in youth mental health.

### Innovations in Family Assessment and Intervention

The assessment of family needs can inform clinical interventions that benefit individual family members, the family system, and the individual diagnosed with the mental health disorder. Several domains of family assessment, however, require greater attention and innovation.

[1] Here we refer collectively to people engaged in supporting young individuals (e.g., parents, siblings, friends, teachers, etc.) as "families."

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Ecologically valid assessment methods have been widely utilized to assess the daily lives of patients with mental health disorders, but surprisingly little light has been shed on the everyday lives of families supporting a young person recovering from severe mental ill-health (Myin-Germeys et al. 2009). Experience sampling and emerging passive sensing methods (Cornet and Holden 2018) could provide clinically useful data regarding the problems faced by families, most notably their daily interpersonal challenges when communicating with their young person.

The physical health of families has also been largely ignored by clinicians and researchers in youth mental health. Early reports have suggested that families of early psychosis patients are frequently overweight, with high rates of hypertension, and elevated risk for type 2 diabetes (Poon et al. 2018). At the upper end of the age spectrum, it is known that the chronic stress in caring for a relative with dementia is associated with a range of physiological markers of disease, including dyscoagulation, inflammation, cell aging, and changes in immune function, compared with controls (Fonareva and Oken 2014). Embedding family health assessments in research and encouraging assessments for families in youth mental health services is worthy of consideration with the aim of prevention of disease in these populations.

Intervening with families in youth mental health offers a window of time in which intensive interventions can maintain the young person's developmental trajectory and prevent the long-term consequences of stress for family members.

There are several possible strategies to refine and extend family interventions. For example, while the targeting of "high expressed emotion" has been important for the prevention of relapse, novel models of the interactions between the family environment and patient outcomes might prove fruitful. These include the early identification of families most at risk of depression and chronic stress, as well as the association with depleted caregiving and modeling of self-efficacy for the young person. The identification of endophenotypes for mental health disorders raises the prospect of interventions for multiple family members that target transdiagnostic processes; for instance, emotional dysregulation, which is linked to personality (Gunderson et al. 2018), mood, and other disorders, is highly likely to compromise the effectiveness of the family system in solving complex interpersonal problems, especially if shared by multiple family members.

The critical issue of access to effective interventions calls for major innovations in available modes of delivery. An online model of family intervention, "moderated online social therapy," was specifically developed to integrate online therapy content with expert and peer moderation within a social networking environment, available 24 hours a day from any internet-enabled device (Gleeson et al. 2017b). An RCT is currently in progress to evaluate the effectiveness of this model for carers of youth recovering from psychosis (Gleeson et al. 2017a). A major added advantage of this model is that it can efficiently

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support relatively large numbers of carers who are dispersed across geographical regions, which is especially important for low-prevalence disorders, where carers are potentially at greater risk of stigma and social isolation and where experts might be in short supply. Our model also integrates a role for carer peer support workers, an element that we argue is ripe for closer empirical investigation, with good prospects for cost-effective dissemination.

### Critical Targets That Have Been Overlooked

To date, family-based interventions have targeted relapse prevention and family levels of stress and burden. Although these are important targets, which we ourselves have pursued (Gleeson et al. 2010), there is an urgent need to develop and evaluate interventions that support families as they address normative parenting goals, such as how to best support a young person who is recovering from severe mental illness to maximize their personal independence, meaning in life, connectedness with others, and to establish a purposeful life. These are, in short, components of eudaemonism, which have oddly eluded the attention of researchers and clinicians alike in youth mental health (Ryff and Keyes 1995).

The issue of abuse perpetrated by family members remains an important controversy in youth mental health. Recent reviews by members of our group confirm that abuse is implicated in raising the risk for psychosis. However, significantly more work needs to be done in formulating effective approaches for working with family members, both perpetrators and victims, in these situations.

### Specific Populations Ignored

There are specific populations of families that have been almost entirely overlooked by researchers and clinicians in youth mental health. Carers of youth with borderline personality disorder have been identified as the most distressed of all carers, given the interpersonal features of the disorder (Bailey and Grenyer 2014). Here, the development of a specific carer intervention would be timely in light of the emergence of an effective youth model for borderline personality disorder (Chanen et al. 2017). Orygen has developed a promising pilot intervention for this group (Pearce et al. 2017), which we plan to extend to a larger trial.

Parents of youth living with gender dysphoria are another population that faces significant stress. Support for these carers might prevent adverse outcomes in their children (Gregor et al. 2016; Hasan et al. 2017).

Other populations include First Nations families that are caring for young people with severe mental disorders, as well as families isolated in rural or remote locations. This is especially true for countries such as Australia and Canada, which have very isolated communities.

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In short, the digital era offers the promise of addressing geographical and demographic obstacles to provide access for specific populations with identifiable needs.

### The Broader Perspective

Contemporary models of family interventions were largely developed out of behavioral and cognitive therapy models in the 1970s and 1980s (Falloon 1988). Little consideration has been given in family research in youth mental health to the effects of secular trends in family environments. For example, in Western-developed nations, there is an expanding timeline for young adults who remain economically dependent on their parents. In addition, the age of first-time parents has been rising over the previous decades, and patterns of workforce participation have changed significantly from what they were 30 years ago, when policies like deinstitutionalization first effected a shift in the burden of care to families in the community. In addition, the structure of families has changed: family size is smaller, there are more blended families, and increasing numbers of same-sex parents are raising children.

Over the last 10–20 years, global economic changes have caused rapid cultural changes in younger generations from emerging economies. Previously, families in these societies were especially supportive and protective of relatives with severe mental health disorders, compared with Western-industrialized contexts.

These large-scale secular trends raise important questions and issues for researchers and clinicians alike in youth mental health. Since pressure on families is unlikely to reduce, researchers and clinicians will need to provide solutions to the local and global problems that continue to emerge.

## Transdiagnostic Biomarker-Guided Intervention

### Supplementation with Omega-3 Fatty Acids to Promote Mental Health in Youth as an Exemplar Model

Pharmaceutical interventions in youth have been limited by lack of efficacy and incidence of adverse events (Bridge et al. 2007; Hetrick et al. 2010). Given the paucity of new drug developments for psychiatry in recent years, alternative biological treatments merit investigation, in particular agents that are more benign and therefore feasible for early intervention (Amminger et al. 2017). There is also a need for pluripotent treatments that can influence core biological processes, such as monoaminergic (Sublette et al. 2004), dopaminergic (Sublette et al. 2014) and serotonergic neurotransmission (Freeman et al. 2006; Garland and Hallahan 2006), oxidative stress, and inflammation. Such treatments are potentially relevant for illness progression transdiagnostically (Berk et al. 2011). In the case of omega-3 fatty acids (n3PUFA), abnormally low

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levels are consistently seen across psychiatric diagnostic categories (Assies et al. 2010; Garland and Hallahan 2006; Parletta et al. 2016a, b; Reddy et al. 2004; Rice et al. 2015), providing a strong biological rationale for supplementation. Furthermore, important for both early intervention and for treatment in youth, there are minimal side effects to n3PUFA (Schlögelhofer et al. 2014). This high margin of safety coupled with an emerging broad therapeutic profile, and evidence of abnormally low levels in people with a range of mental health problems, supports the investigation of its efficacy as novel biomarker-guided therapy for young people with emerging mental health conditions across diagnostic categories.

## Long-Chain n3PUFA Polyunsaturated Fatty Acids

Polyunsaturated fatty acids (PUFA) can be classified into n3 and n6 fatty acids, and have numerous and diverse functions in the human body. They are part of phospholipid molecules, the main structural building blocks of cell membranes. PUFA are bioactive molecules that play central roles in a broad range of physiological functions. For example, two particularly important PUFA, eicosapentanoic acid (EPA) and arachidonic acid, are key players in signal transduction, ion transport, and receptor sensitivity (e.g., for serotonin, dopamine, endocannabinoids), as well as precursors in the biosynthesis of the eicosanoids (prostaglandins, leukotrienes, thromboxanes), which mediate the inflammatory response (Mossaheb et al. 2012). Another key PUFA, docosahexaenoic acid (DHA), serves as a precursor for the docosanoids (resolvins, neuroprotectins), which have a neuroprotective effect. The brain is highly enriched with DHA and their derivatives, which regulate biological processes such as neurotransmission, neuroplasticity, and neuroinflammation, and thereby mood and cognitive function (Lin et al. 2017; Piomelli et al. 2007; Su et al. 2015). Moreover, n3PUFA may modulate neurotrophins (Venna et al. 2009), which might be a direct mechanism to mediate neurogenesis and antidepressant effects (Blondeau et al. 2009). Finally, elevated plasma triglyceride level is a cardiovascular risk factor (Hokanson and Austin 1996): n3PUFA have long been known to lower plasma triglyceride along with a variety of other drugs such as fibrates and statins (Patel and Budoff 2016).

## n3PUFA Deficiency in Psychiatric Disorders

Low levels of n3PUFA have been consistently reported in psychiatric populations compared with healthy controls across diagnostic categories, including major depressive disorder (Assies et al. 2010), bipolar disorder, anxiety disorders (Thesing et al. 2018), borderline personality disorder (Garland et al. 2007), schizophrenia (Reddy et al. 2004), at-risk mental state for psychosis (Rice et al. 2015), autism spectrum disorders (Parletta et al. 2016a), and attention deficit hyperactivity disorder (Parletta et al. 2016a). These findings are supported

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by large-scale epidemiological studies. Considering that fish are the principal source of EPA and DHA, Hibbeln (1998) reported that the variation in rates for major depression across countries inversely correlated with national fish consumption. In another study, a 17-year follow-up of 256,118 Japanese people demonstrated that daily fish-eating had a positive effect in reducing the risk of death from suicide, compared with individuals having a nondaily consumption (Hirayama et al. 2004). A survey of 3204 adults in Finland found that infrequent fish consumption was associated with depressive symptoms in women, and a similar trend was noted in men (Tanskanen et al. 2001). A similar inverse relationship between fish consumption and prevalence rate has been demonstrated for bipolar affective disorder (Noaghiul and Hibbeln 2003), although the same study did not find a relationship between fish consumption and the prevalence of schizophrenia. However, there is compelling evidence supporting an association between fish consumption and subthreshold psychotic phenomena. Hedelin et al. (2010) conducted a study among 33,623 women in Sweden to evaluate the association of dietary intake of PUFA with the prevalence of positive psychotic symptoms. Among their many findings, the authors reported a risk ratio of 0.45 (95% CI 0.31–0.66) for high levels of psychotic symptoms for participants who consumed fish on three to four times per week.

## Low Levels of n3PUFA Are a Risk Factor for Cardiovascular Disease

An n3 index for cardiovascular health was developed by Harris and von Schacky (2004). The n3 index is the sum of EPA and DHA in erythrocyte membranes and is expressed as a percentage of total erythrocyte fatty acids. They first established erythrocyte levels of EPA+DHA as a valid biomarker of n3PUFA status (Harris 2008). By pooling together results from prospective studies and RCTs, they identified that an n3 index <4% in erythrocyte membranes was associated with the highest risk of mortality from coronary heart disease, whereas levels >8% conferred the greatest cardioprotection. Therefore, the n3 index was proposed as a useful biomarker to estimate risk of mortality from coronary heart disease and provide targets for reducing mortality risk (von Schacky 2009). The direct roles of n3PUFA, particularly DHA (Serhan et al. 2011), in brain function and the growing evidence of their ability to improve psychiatric symptoms suggest that the n3 index might similarly provide a useful target for estimating risk of mental illness and targets for treatment.

## Treatment Studies with n3PUFA in Psychiatric Disorders

### *Trials in Major Depressive Disorder and Anxiety Disorders*

Trials evaluating efficacy of n3PUFA supplementation in major depression report conflicting findings (Bloch and Hannestad 2012; Hallahan et al. 2016; Sublette et al. 2011). Among participants with major depressive disorder,

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however, EPA-predominant formulations (>50% EPA) demonstrated clinical benefits, compared with placebo, whereas DHA-predominant formulations (>50% DHA) did not (Hallahan et al. 2016). Notably, the majority of trials have been conducted in adult populations, with n3PUFA as an adjunct to antidepressant medication and without selecting participants with abnormally low n3PUFA levels. Interestingly, one proof-of-concept RCT of n3PUFA in people with major depressive disorder found that participants with specific combinations of inflammatory markers were more likely to respond to EPA treatment and less likely to respond to placebo treatment (Rapaport et al. 2015). This study highlights the importance of biomarker screening to determine a participant's eligibility for trials and better treatment outcomes.

Anxiety disorders are frequently comorbid with depression. This raises the possibility that n3PUFA levels might contribute to the pathophysiology of both conditions (Ross 2009). In support of n3PUFA supplementation in people with anxiety, a study from Israel reported decreased n3PUFA levels in nondepressed patients with social anxiety disorder (Green et al. 2006). Liu et al. (2013b) found the presence and severity of comorbid anxiety in people with depression were associated with the lowest n3PUFA levels. The Netherlands Study of Depression and Anxiety showed that currently depressed patients, especially those with comorbid anxiety, had n3PUFA levels lower than those in remission or in healthy controls (Thesing et al. 2018). One RCT showed that n3PUFA supplementation lowered anxiety symptoms in medical students (Kiecolt-Glaser et al. 2011), which provides the first evidence that n3PUFA might have anxiolytic benefits.

### *Trials in Youth with At-Risk Mental State for Psychosis*

A 12-week RCT of supplementation with n3PUFA reduced the risk of progression to psychotic disorder in 81 young people with at-risk mental state over a 12-month period, compared with a placebo (Amminger et al. 2010). A longer-term follow-up of this trial found that the brief intervention with n3PUFA was still effective. Compared with placebo, n3PUFA prevented transition to full-threshold psychotic disorder and led to sustained symptomatic and functional improvements for seven years (median) (Amminger et al. 2015). In addition to these trial results, both (negative) correlations between n3PUFA and psychopathology (Kim et al. 2016), along with a large effect size deficit for n3PUFA (compared with healthy adolescents) observed in patients with an at-risk mental state, provide a further rationale for supplementation as early intervention for incipient psychotic symptoms (Rice et al. 2015). Furthermore, a high ratio of n6 to n3PUFA, which indicates a relative deficiency of n3PUFA, is thought to have adverse health effects (Simopoulos 2011). A higher n6 to n3PUFA ratio at baseline has been found to predict mood disorders at longer-term follow-up (Berger et al. 2017).

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Two large-scale studies have tried to replicate these findings. In the NEURAPRO study of 304 individuals with an at-risk mental state for psychosis (McGorry et al. 2017), 153 received n3PUFA and 151 received placebo for 6 months. No significant group difference was observed for rates of transition to psychosis. A lower than expected psychosis transition rate (11% vs. 25%) might have prevented a test of the main hypothesis; the trial also failed to show effects in favor of n3PUFA on secondary outcome measures. An important limitation of NEURAPRO (and all n3PUFA RCTs) is that the use of n3PUFA supplements unrelated to the study cannot be excluded (James et al. 2014). Therefore, secondary analyses were conducted using cell membrane-level change pre- to post-supplementation as objective measures of n3PUFA intake. Again, when analyzed as a single cohort, no association was observed between n3PUFA levels and transition to psychosis. However, increase of n3PUFA was found to be significantly related to functional and symptomatic outcome measures at 6 and 12 months (Amminger et al. 2018). In contrast to the RCT analysis, this secondary analysis, using biomarker information, showed that an increase in erythrocyte n3PUFA correlated with better clinical outcomes, thus confirming the findings of Amminger et al. (2010).

Preliminary data are available from a second, independent n3PUFA supplementation replication RCT in individuals from the North American Prodrome Longitudinal Studies (NAPLS) (Cadenhead et al. 2017). Of the 127 "clinical high-risk" patients recruited into the trial, the rate of transition to psychosis was low (10%) over 24 months of follow-up, without statistical difference between n3PUFA and placebo groups. However, the researchers noted cardiometabolic abnormalities were prevalent at baseline in this cohort of young people, and they found significant evidence that those with low n3PUFA in their diet were statistically more likely to have converted to a psychotic disorder by study end (Cadenhead et al. 2017).

### *Post Hoc Analysis of the NEURAPRO RCT*

Therapeutic effects of n3PUFA might be stronger in subgroups characterized by certain biological or phenotypic markers (Kraemer 2016); for example, low n3 index at baseline. The post hoc analysis of the NEURAPRO RCT posed two questions:

1. Is n3PUFA supplementation specifically effective in participants characterized by low n3 index at baseline?
2. Do effects differ between participants randomized to n3PUFA or placebo?

In NEURAPRO, erythrocyte fatty acid data were collected in 285 out of 304 (94%) participants (mean age = 19.1 yr, SD = 4.6). The mean n3 index at baseline in the sample was 2.96% (SD = 1.10; median = 3%). This is 40% lower than the average n3 index (5%) in the Australian population (Swierk et

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al. 2011). The median n3 index of 3% places theoretically half of this cohort of young people at a substantially elevated longer-term risk of premature death from coronary heart disease (Parletta et al. 2016b; von Schacky 2009). This view and the very high rate of youth with abnormally low n3PUFA levels in NEURAPRO are consistent with the fact that people with mental health problems die at a significantly younger age (Thornicroft 2011).

To show specific efficacy of n3PUFA supplementation in people with low levels, a median split was used to group participants with low and high n3 index at baseline. Analyses tested whether change in the n3 index (an objective measure of n3PUFA intake), over the 6-month treatment period in NEURAPRO, was differentially associated with clinical improvement in groups characterized by an n3 index of <3% versus ≥3% at baseline. The Clinical Global Impression–Improvement (CGI-I) scale (Busner et al. 2009), ranging from one to seven (lower scores indicate more improvement as compared with baseline), was used. A score of one or two (i.e., very much or much improved) reflects a substantial, clinically meaningful improvement in illness severity. Figure 10.1 shows that in the <3% group, individuals with much or very much clinical improvement, when compared with individuals with less favorable outcomes, were characterized by a significantly higher increase of their n3 index (mean = 1.5, SD = 1.3 vs. mean = 0.7, SD = 1.7; mean difference = –0.8, P = 0.015); more n3PUFA intake between baseline and 6 months was associated with better clinical outcome. In the ≥3% group, this association was not observed. These findings suggest that n3PUFA supplementation should target individuals with low n3 index (<3%), who are also at risk of coronary heart disease and might benefit in terms of both mental and physical health.

To further elucidate the observed treatment effect in NEURAPRO participants with low n3 index (<3%), the same test was conducted separately in the fish oil and the placebo groups. Better clinical outcomes were consistently associated with a higher increase of the n3 index for both groups: for fish oil, the mean difference was –1.0 whereas for the placebo, the mean difference was –0.8 (Figure 10.2). This analysis suggests that treatment effects of n3PUFA in NEURAPRO occurred in both treatment arms. It also indicates the importance of utilizing biomarker information to determine the efficacy of n3PUFA supplementation versus placebo.

Clinical trial evidence suggests that n3PUFA are safe and well tolerated (Freeman et al. 2006; Schlögelhofer et al. 2014). Most commonly occurring, but clinically rarely significant, are mild gastrointestinal symptoms (e.g., a fishy aftertaste, indigestion). It has been suggested that the potential antithrombotic effect of fish oil might theoretically increase the risk for bleeding, which might be a safety concern for individual participants. However, clinical trial evidence has not supported increased bleeding with n3PUFA intake, even when combined with other agents (such as aspirin or warfarin) which might also increase bleeding (Bays 2007). Differential effects on metabolic parameters, most of which appear to be beneficial, have also been reported (Mossaheb et al. 2015).

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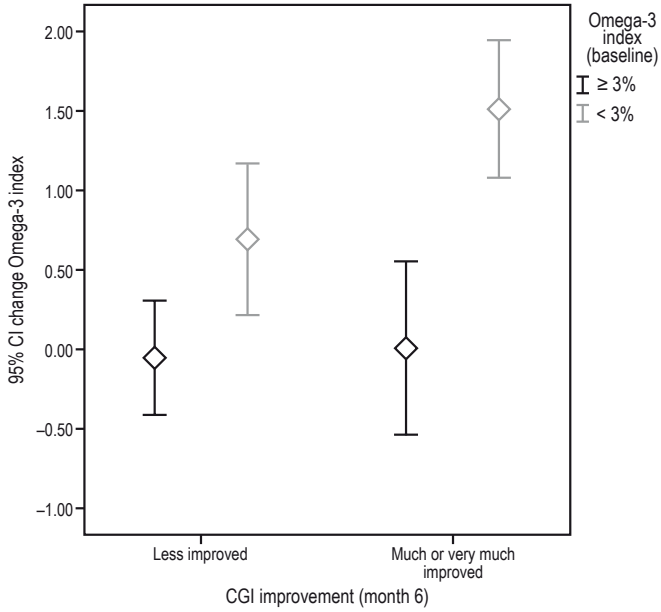


**Figure 10.1** Change in omega-3 index between baseline and month 6 in participants with low or high baseline omega-3 levels by clinical improvement groups.

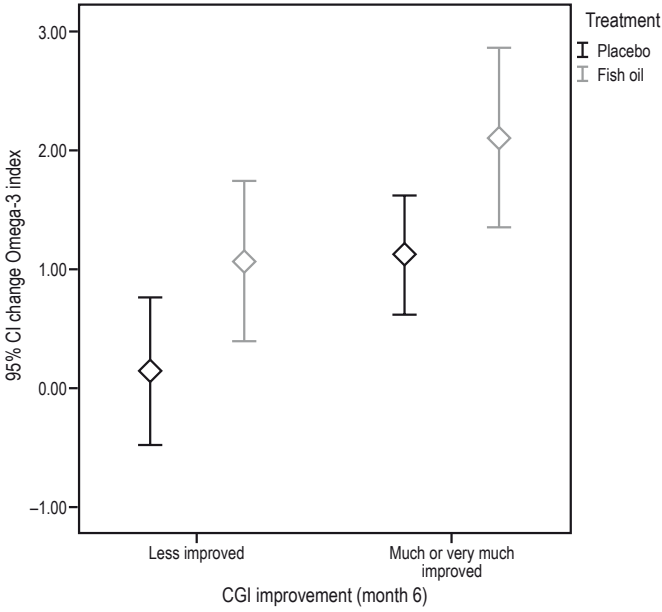


**Figure 10.2** Change in omega-3 index between baseline and month 6 in participants who received fish oil or placebo by clinical improvement groups.

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A recently developed capillary dried blood spot test can be used to quantify levels of n3PUFA and other relevant fatty acids in erythrocytes (e.g., n6PUFA) (Liu et al. 2014a). This has strong practical and cost advantages over conventional methods because of the need for remarkably lower blood volumes and easier shipping and storage at ambient temperatures.

## Conclusions

Interventions and mental health services for youth are mired in failures of relapse prevention, social recovery, innovation, access to services, and research translation. Three avenues for progress lie in novel digital interventions, broadening the scope of family assessment and intervention, and transdiagnostic biomarker-guided intervention.

Integration of digital interventions into mainstream youth mental health services aims to create a new paradigm, fueled by fast innovation and research translation. Successful implementation has the potential to revolutionize the field through online social media and mobile technology, novel and evidence-based psychological models, and new blends of multidisciplinary expertise that will lead to new interventions designed to transform clinical practice, rather than merely translating existing face-to-face interventions into an online mode of delivery.

Digital and other technologies can also transform family intervention by providing ecologically valid family assessment. Family intervention in youth mental health needs to move away from a narrow focus on psychotic disorders, patient symptoms, and relapse and toward the inclusion of overlooked populations and transdiagnostic processes as well as family burden and the mental and physical health of families, which have the potential to yield major reductions in carer and disease burden.

Finally, transdiagnostic prevention and treatment of severe psychiatric morbidities (e.g., anxiety, psychotic, mood, and personality disorders) is a promising avenue for reducing the burden, stigmatization, and economic consequences of these disorders. A 20-year mortality gap for men, and 15 years for women, is still experienced by people with mental ill-health in high-income countries (Thornicroft 2011). Cardiovascular and metabolic risk factors are prevalent among people with mental health problems, even at a young age (Cadenhead and Mirzakhanian 2016).

Based on the existing literature and new observations presented here, n3PUFA supplementation with fish oil is proposed as a prototype for transdiagnostic biomarker-guided intervention for young people with mental health problems. This proposal introduces a new paradigm in primary health care by using easily accessible biomarker information to target an intervention with an excellent side effect profile to a group most likely to benefit for a broader range of health outcomes.

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