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Single-Subject Designs and Practice-Based Research in Palliative Care: A Letter to the Editor.

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Dear Dr. Portenoy,

Randomized controlled trials (RCTs) have advanced pain and symptom management in the context of chronic illnesses, and are regarded as the ideal designs to guard against threats to internal validity. These designs also enable researchers to obtain unbiased estimates of intervention effects compared to control conditions. However, overreliance on RCTs may stifle research progress if resources are limited, clinically meaningful differences are small, or participants differ from those who do not consent, are excluded, or leave the study prior to completion.[1]

The RCT's challenges are compounded in palliative medicine when patient resources are depleted and personnel are strained. In one trial, the senior author succeeded in enrolling only 0.3% of patients approached. In other trial, Van Scheppingen (2014) estimated that 17-person hours were required to recruit each patient into a supportive oncology study.[2] If RCTs are not feasible or have not been conducted to inform practice, an alternative but complementary approach is to conduct practice-based research. It is argued that single-subject research designs (SSRD) are viable but underutilized tools for treatment outcome research in palliative medicine.[3] Whereas the RCT seeks to answer *Which treatment is better for subjects on average?,* SSRDs seek to answer *Does this treatment work for this particular individual in this particular situation?* Therefore, the SSRDs have substantial potential for advancing personalized medicine in palliative care.[4]

SSRDs have been applied to common sources of suffering seen in palliative care, and are applicable to the investigation of medical illnesses. SSRDs and related small-n designs have

played pivotal roles in elucidating principles of behavior and behavioral pharmacology, and for testing interventions for anxiety, pain, conditioned nausea, and blood pressure.[4–6] SSRDS have also been used study interventions for agitation, and cognitive problems related to neurocognitive disorders. Despite the clear applicability to problems of pain and symptom management, these designs are not routinely implemented in palliative care research and practice.[3,4]

Kazdin outlined the essential features of SSRDs including repeated assessment of behavior, establishment of within-subject control conditions, and stability in the behavior of interest.[7] Whereas group designs use pre, post, and follow up assessments, SSRDs assess behavior in a continuous fashion over minutes, days, and weeks. Experimental control is established within the subject, typically with a baseline assessment phase (A) that is collected before the intervention is applied (B). Mean differences, variation, and slope of behavior are compared across conditions. Data are typically analyzed with visual inspection, but statistical methods can help mitigate biased interpretation.

The components of SSRDs can be configured in plethora of ways. Figure 1 depicts hypothetical data to illustrate several of these designs. Figure 1A is an A-B-A-B or Reversal design with hypothesized data for a patient with joint pain partially attributed to use of aromatase inhibitors. The baseline phase (A) characterizes a boom-and-bust activity pattern common in the context of chronic pain where sudden increases in physical activity are followed by increased pain and downtime. The intervention phase (B) introduces activity pacing where the patient is encouraged to gradually increase walking, but to stop before walking causes more than minimal pain. The patient also has a brief call with her nurse on Mondays and Thursdays for accountability and encouragement. Minutes walking stabilizes near the patient's walking goal

during the final week of the intervention. The decision is made to remove the phone calls. The walking goal is maintained for several days after the phone calls stop (return to baseline), but without the accountability the boom-and-bust pattern returns. Both greater degrees of variation, and downward slopes are evident during the baseline phases. By comparison, walking is more consistent and has an upward slope during the intervention phases.

Within the RCT framework, random assignment and control conditions guard against threats to internal validity (maturation, history). SSRDs guard against threats to internal validity of the cause-effect relationship through replication within or across subjects. Returning to the example data above in Figure 1A it is possible that the upward trend in minutes walking beginning at day eight could be explained by history effects. For example, a pleasant change in weather or augmented medication regimen could increase activity. However, the argument for history effects becomes less plausible because walking systemically changes with the removal and replication of the intervention.

In many cases it is not feasible or ethical to remove a treatment (e.g. patient learned a new symptom management skill and is unlikely to forget it). A multiple baseline design -which has some similarities to the waitlist control group design - can be used as an alternative. In this SSRD, several participants are exposed to an A-B design. The first patient to achieve a stable baseline receives the intervention, while others continue in the baseline condition. Patients are included in the intervention in successive fashion. Concerns for history effects and other threats are mitigated when change occurs during interventions that are introduced after varying baseline intervals, rather than simultaneously. A caveat is that this design moves in the direction group-based designs, makes inference about group level effects, and may be less feasible in routine clinical practice when several baselines must be synchronized across patients.

In practice, multiple palliative interventions are delivered in close proximity creating difficulty in isolating the effective components of treatment. In the alternating treatments design, a baseline is collected before treatments are alternated and pitted against one another. Figure 1B depicts hypothesized frequency of agitated behavior by a patient with end stage renal disease. Agitated behavior increases over baseline. Two competing hypotheses are that 1) the patient is not managing stress well and would benefit from mindfulness and 2) separation anxiety is triggering panic, and the patient would benefit from company from a volunteer. Both interventions are delivered, alternating each day. Eventually, the data from the two conditions diverge and it is decided that volunteer visits are more beneficial. Figure 1C depicts an alternative approach where mindfulness is added first (B) and maintained with the inclusion of daily visits from a hospice volunteer (B+C).

Barriers and Benefits of SSRD implementation

SSRDs are particularly beneficial for chronic conditions where *one size does not fit all*.[4] In our experience, chronic symptoms and poor response to general treatment are precisely why patients are referred for palliative care. The primary barriers to implementation of SSRDs may be lack of expertise and misconceptions among clinicians, educators and reviewers. For example, SSRDs are perceived by some clinicians as too time intensive.[1,4] However, inefficiencies in current practice occur when trial-and-error symptom management is implemented by one or more clinicians. The time for implementation of SSRDs is ripe as clinicians are already formulating causal hypotheses about the treatments they deliver, and patient reported outcomes are being tracked through self-report as part of distress screening programs. In the clinic, SSRDs foster more intentional approach to clinical hypothesis testing and treatment response.

SSRDs may be contraindicated when treatment response lacks significant individual variation, and when an acute course of symptoms precludes repeated assessment of symptoms or behaviors. SSRDs are also impractical when treatments effects occur after significant latencies because the causal lags become increasingly difficult to discern from history effects and other confounds. A similar concern arises when treatment effects are slow to washout (e.g. learning from behavior therapy, effects of SSRIs). In this case, reversal designs that remove the treatment, or alternating treatment designs that rotate them are unlikely to yield clear functional relationships between treatment and outcome.

A final benefit to consider is the sense of compassion satisfaction clinicians experience when seeing positive response to treatment. Similar to psychotherapy practice, palliative medicine may be difficult to learn from because many processes are in flux, and secondary loss may overshadow the fulfilling aspects of work. SSRDs have the potential to highlight the times where “unfixable” chronic conditions get systematically better, albeit sometimes in small or context-dependent ways.

Sincerely,

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Figure 1. Panel A. Hypothetical data for minutes spent walking across days during baseline (filled circles) and activity pacing (open circles) conditions. Panel B. Hypothetical data for percentage of observations involving patient agitation across days during baseline (filled circles), mindfulness practice (open circles), and volunteer visitation (open triangles), where mindfulness practice and volunteer visitation alternated daily. Panel C. Hypothetical data for percentage of observations involving patient agitation across days during baseline (filled circles), mindfulness practice (open circles), and mindfulness practice + volunteer visits (open triangles).